**STUDY PROTOCOL**

# Kinetics of physiological and symptomatic responses to CardioPulmonary Exercise Testing (CPET) in subjects with persistent exercise intolerance after COVID-19: an Open-Source Exercise Network

| | |
|---|---|
| **Study data manager** | Association pour la Complémentarité Connaissances et Pratiques de la Pneumologie (aCCPP) |
| **Coordinator**<br><br>**Principal investigators** | Prof. Bernard Aguilaniu (Univ. Grenoble Alpes)<br><br>Prof. Pierantonio Laveneziana (Univ. Hospital La Pitié-Salpétrière, Paris)<br>Prof. Frédéric Costes (Univ. Hospital of Clermont-Ferrand) |
| **Investigators** | Pulmonologists, Cardiologists and Physiologists involved in the realization and the diagnostic interpretation of the Cardio Pulmonary Exercise Testing -CPET) that it is within public or private structures (Univ. Hospitals, General Hospitals, private practices or mixed).<br><br>About 40 investigators are expected. |
| **Protocol date** | June 9, 2023 |
| **Protocol version** | 1.2 |

***Synopsis***

| | |
|---|---|
| **Title of the study** | **Kinetics of physiological and symptomatic responses to CardioPulmonary Exercise Testing (CPET) in subjects with persistent exercise intolerance after COVID-19: an Open-Source Exercise Network** |
| **Study data manager** | Association pour la Complémentarité Connaissances et Pratiques de la Pneumologie |
| **Coordinator**<br><br>**Principal investigators** | Prof. Bernard Aguilaniu University Grenoble Alpes<br><br>Prof. Pierantonio Laveneziana Univ. Hospital La Pitié-Salpétrière, Paris<br>Prof. Frédéric Costes Univ. Hospital of Clermont-Ferrand |
| | Coordinator Prof. Bernard Aguilaniu (Univ. Grenoble Alpes)<br><br>**Members/Investigators:**<br>Prof. Pierantonio Laveneziana - Univ. Hospital La Pitié-Salpétrière Paris<br>Prof. Frédéric Costes - Univ. Hospital Clermont-Ferrand<br>Dr. David Debeaumont - Univ. Hospital Rouen<br>Dr. Yan Martinat - Centre Médical Parot Lyon<br>Dr. Frija-Masson Justine - Univ. Hospital Bichat Paris<br>Dr. Motiejunaite Justina - Univ. Hospital Bichat Paris<br><br>**Members/Consultants:**<br>Prof. Anestis Antoniadis - IMAG Univ. Grenoble Alpes<br>Prof. François Péronnet - Univ. Montréal-Canada |
| **Centers and investigators** | Pulmonologists, Cardiologists and Physiologists involved in the realization and the diagnostic interpretation of the Cardio Pulmonary Exercise Testing -CPET) that it is within public or private structures (Univ. Hospitals, General Hospitals, private practices or mixed).<br><br>About 40 investigators are expected. |
| **Current status** | Since the first wave of COVID-19, pulmonologists, cardiologists and physiologists are regularly consulted for intolerance to exercise expressed by dyspnea and/or frank fatigability sometimes associated with muscular or thoracic pain. When these complaints persist beyond 3 months after the first symptoms, it is legitimate to perform a CPET:<br>• Either to evaluate the functional impact of an identified organ deficiency (e.g. myocarditis, pulmonary fibrosis, etc.),<br>• Or, in the absence of formal arguments for an identified organ deficiency, to observe possible abnormalities in physiological responses during an incremental exercise test, likely to explain the persistence of symptoms and intolerance to exercise.<br><br>The recent literature highlights the presence of non-specific ventilatory and cardio-circulatory abnormalities leading to various physio-pathological observations. These reports concern today relatively small numbers of patients mixing subjects whose clinical forms of COVID, comorbidities and habitus are very diverse. Moreover, the hypotheses or conclusions proposed by these studies are influenced by the medical specialty of the practitioner who observes them.<br>Thus, it seems necessary to collect a very large number of clinical and physiological observations in order to draw up a factual report of the disorders observed without any interpretative preconception.<br>It is reasonable to assume that, with time, health professionals will be frequently confronted with patients with exercise intolerance after COVID-19 and that the management of the disease will be more codified. For this, it seems necessary to collect and secure as much data as possible in order to improve the understanding of persistent symptoms and in particular the potential diversity of phenotypic presentations. |
| **Objectives** | **<u>Primary objective</u>:** |

| | |
|---|---|
| | **Physiological responses and symptoms during CPET in subjects diagnosed with COVID who have persistent symptoms responsible for exercise intolerance**<br>Homogeneous patient subgroups will consider:<br>• the initial clinical presentation of COVID,<br>• any persistent symptoms other than exercise intolerance,<br>• clinical characteristics prior to COVID-19 infection (co-morbidities – regular habitual physical activity).<br><br>**<u>Secondary objectives:</u>**<br>- To model the kinetics of ventilatory pattern responses in order to characterize the behavior of excessive hyperventilation and, possibly, chaotic breathing.<br><br>- To test, through different statistical models, the possibility of predicting the persistence of dyspnoea as a function of exercise variables, pre-existing clinical data of the COVID, clinical presentation of the acute COVID. |
| **Concerned population** | **Inclusion criteria:**<br>• Age ≥ 18 years<br>• Patients with persistent symptoms 3 months after the onset of COVID-19 infection, regardless the severity of the initial illness<br>• Patients with an ICU stay, primarily following rehabilitation management; that is, in practice, at least 6 months after COVID<br>• Patients followed by a pulmonologist, cardiologist or physiologist in a public or private facility or in private practice, allowing for CPET<br>• Patients who have performed a CPET before December 31, 2022<br>• Patients informed of the possible anonymized processing of the data collected during CPET for research purposes; and who gave informed consent<br>**Exclusion criteria:**<br>• Age < 18 years<br>• Patients unable to perform CPET for locomotor reasons<br>• Patients with severely reduced functional work capacity<br>• Patient deprived of liberty by judicial or administrative decision<br>• Patients unable to give informed consent |
| **Study type and methodology** | French-speaking, multicentric, observational, descriptive cohort study with retrospective data collection, not affecting the management of patients and in line with the French MR004 reference methodology.<br><br>The following processes are defined in this protocol:<br>• on-site collection of clinical and physiological data from patients process;<br>• anonymization and migration process of these data (collected on each investigation site) to the centralized CPET-studies.com platform which will return an anonymized file dedicated to statistical analysis. |
| **Recruitment** | **<u>Investigator Recruitment</u>**<br>From June 1, 2022, pulmonologists, cardiologists and physiologists performing CPET in public or private structures (Univ. Hospital, General Hospital, private practice or mixed activity) will be invited to participate in this study.<br><br>**<u>Patient Recruitment</u>**<br>From February 1, 2023, each investigator will be able to identify the files of patients who meet the inclusion criteria of the protocol by going back to January 2, 2020.<br>From February, 2023, each investigator will be able to ensure the migration on the CPET-studies.com platform of clinical and physiological data collected between January 2, 2020 and December, 2023. |
| **Data collection** | **Physiological data collection**<br>Physiological measurements made during CPET (source data) will be stored locally on each investigator's ergospirometer until the time of migration. |

| | |
|---|---|
| | They include continuous recording of ergospirometer measurements and discontinuous recording of blood pressure, symptoms and blood gases.<br><br>In order to get rid of some of the variability of the results the export will only concern the measured data. Additional physiological data will then be obtained by applying the appropriate physiological calculation formulas in a strictly identical way whatever the brand of the ergospirometer. All these data (measured and calculated) will be transformed by the CPET-STUDIES application into a file called *Finalized File.*<br><br>**Collection of clinical data**<br>The clinical data of the patients will be collected on the medical file or a dedicated file (Excel or Word) by each practitioner. They will be filled in by the referring physician who alone knows the name and surname of his patients on the online platform. The identifying data of each patient will then be pseudonymized so that no one other than the referring physician can access them. All data is hosted by a health data host certified for the 6 HDS levels.<br><br>Clinical data are: sex, weight, age, height, date of COVID, physical activities before COVID, comorbidities, COVID-related symptomatology, usual treatments, Hospital Anxiety and Depression Scale (HADS) and Chalder fatigue scale questionnaires.<br><br>**Access to the platform will be secured** by identification with a login and a password<br>The patient's physiological and clinical data will be encrypted and pseudonymized when migrated and/or entered on the CPET-STUDIES.COM platform.<br><br>The content of the Finalized File will then be imported into a database, which contains only the clinical data associated with the patient's pseudonym. |
| **Patient information** | As is commonly done on admission to hospitals, a signed informed consent form will be attached to the administrative and medical file of the patient.<br><br>In the absence of the signed informed consent form, patients who have undergone CPET will be contacted and informed of the modalities of this study, and asked to sign the informed consent form (see *Appendix 1*).<br><br>This will be done as long as it does not involve a disproportionate effort. |
| **Overview and duration of the study** | The data collection will be carried out from February 1, 2023 to December 31, 2023 or during 10 months.<br>The data concerned cover the period from January 2, 2020 to December 31, 2022 (35 months).<br>These data were stored by the investigators on-site as part of their usual practice.<br><br>The migration of locally stored data to the CPET-STUDIES.COM platform will take place between February, 2023 and December 31, 2023. |
| **Data analysis method** | Analyses will be performed using R software, with all required software packages, and JAGS, in their most up-to-date version at the time of analyses.<br><br>No hypotheses will be tested for either the primary or secondary objectives. A descriptive analysis of all evaluation criteria will be performed on the total population and on subgroups to be defined a priori according to the sample.<br><br>The variables collected at the end of the steady state, at maximal exercise, and during recovery (2 min) will be expressed as mean, standard deviation (SD), median, quartiles.<br><br>Modeling of the kinetics of certain variables (VE TV-BF-HR- RER) will be performed and then a mathematical model will be developed to quantify and compare these kinetics between subgroups. Comparisons of kinetics between subgroups will be made using recently developed mixed-effects functional analysis of variance (FANOVA) methods. |

| | |
|---|---|
| | The kinetics of some variables will be expressed as a function of developed power (in watts), metabolic power ($VO_2$ in L/min), ventilatory flow (in L/min), HR expressed in absolute value, in % of the max HR reached and in % of the predicted value according to the formula maxHR = 210-0.65 x age).<br><br>At the request of the scientific committee, additional analyses may be carried out, in particular with regard to the measurement of operating volumes during exercise. |
| **Number of patients** | 1 000 patients with exercise intolerance following COVID are expected. |
| **Financial partners** | Financial support from the Pharmaceutical Group Menarini France and AstraZeneca |

*Table of contents*


***Synopsis*** ..... ***2***

***1. Introduction*** ..... ***9***

***2. Objectives of the study*** ..... ***9***

**2.1. Primary objective** ..... **9**

**2.2. Secondary objectives** ..... **9**

***3. Investigators and organization of the study*** ..... ***9***

**3.1. Study data manager** ..... **9**

**3.2. Coordinating investigator and principal investigators of the study** ..... **9**

**3.3. Steering committee of the study** ..... **9**

Coordinating investigators: ..... 10

Other members: ..... 10

**3.4. Centers and investigators** ..... **10**

**3.5. Management center and statistical analysis** ..... **10**

***4. Design of the the study*** ..... ***10***

**4.1. Constitution of the cohort and data collection** ..... **10**

**4.2. Data migration** ..... **11**

***5. Population of the study*** ..... ***11***

**5.1. Recruitment procedures** ..... **11**

**5.2. Number of Patients** ..... **11**

**5.3. Eligibility Criteria** ..... **11**

**5.4. Exclusion Criteria** ..... **11**

**5.5. Previous and/or concomitant treatments** ..... **11**

***6. Evaluation criteria*** ..... ***11***

**6.1. Primary endpoint** ..... **11**

**6.2. Secondary endpoints** ..... **11**

***7. Procedures of the study*** ..... ***11***

**7.1. Recruitment of pulmonologists, cardiologists, physiologists and patients** ..... **12**

**7.2. Data collection** ..... **12**

7.2.1. Clinical data ..... 12

7.2.2. Physiological Data ..... 12

**7.3. Data transmission and migration** ..... **12**

**7.4. Dissemination or publication of the study results** ..... **13**

***8. Statistical analysis*** ..... ***14***

***9. Sample size*** ..... ***14***

***10. Legal and ethical considerations*** ..... ***14***

**10.1. Ethical considerations** ..... **14**

**10.2. Information to patients** ..... **14**

**10.3. Pharmacovigilance** ..... **14**

**10.4. Protocol amendment** ..... **14**
**10.5. Archiving** ..... **14**
**10.6. Financial Partner** ..... **15**
***Appendix 1: Informed Consent Form*** ..... ***16***
***Appendix 2: CPET post-COVID questionnaire*** ..... ***18***
***Appendix 3: Borg scale*** ..... ***20***
***Appendix 4: Methodology of the CPET*** ..... ***21***
***Appendix 5: HADS questionnaire*** ..... ***22***
***Appendix 6: Chalder faigue scale*** ..... ***23***

List of abbreviations

| | |
|---|---|
| CNIL | Commission nationale informatique et liberté<br>*English: French National Commission on Informatics and Liberty* |
| ECG | Electrocardiogram |
| e-CRF | Electronic case report form |
| SD | standat deviation |
| IC 95 % | Confidence Interval 95 % |
| TLC | Total Lung Capacity |
| FRC | Fonctinal Residual Capacity |
| IC | Inspiratory Capacity |
| $FEV_1$ | Forced Expiratory Volume in 1 sec |
| FVC | Forced Vital Capacity |
| SVC | Slow Vital Capacity |
| Tlco | Transfer Lung carbon monoxyd |
| HR | Heart rate |
| BF | Breathing Frequency |
| 6MWT | 6 min walking Test |
| CPET | Cardio Pulmonary Exercise Testing |
| $VO_2$ | Oxygen |
| RER | Respiratory Exchange Rate |
| VA | Alveolar Ventilation Flow |
| VE | External Ventilatory Flow |
| RV | Residual Volume |
| TV | Tidal Volume |

## *1. Introduction*

Since the first wave of COVID, pulmonologists, cardiologists and physiologists are regularly consulted for intolerance to exercise expressed by dyspnea and/or frank fatigability sometimes associated with muscular or thoracic pain. When these complaints persist beyond 3 months after the first symptoms, it is legitimate to perform a CPET:

- Either to evaluate the functional impact of an identified organ deficiency (e.g. myocarditis, pulmonary fibrosis, etc.),
- Or, in the absence of formal arguments for an identified organ deficiency, to observe possible abnormalities in physiological responses during an incremental exercise test, likely to explain the persistence of symptoms and intolerance to exercise

The recent literature highlights the presence of non-specific ventilatory and cardio-circulatory abnormalities leading to various physio-pathological observations. These preliminary reports concern today small numbers of patients mixing subjects whose clinical forms of COVID, comorbidities and habitus are very diverse. Moreover, the hypotheses or conclusions proposed by these studies are influenced by the medical specialty of the practitioner who observes them.

Thus, it seems necessary to collect a very large number of clinical and physiological observations in order to draw up a factual report of the disorders observed without any interpretative preconception.

## *2. Objectives of the study*

*2.1. Primary objective*

**Kinetics of physiological responses and symptoms during CPET:** to describe by homogeneous subgroups of patients, the physiological responses and symptoms during CPET in COVID-19 subjects with persistent symptoms responsible for exercise intolerance.

Homogeneous patient subgroups will consider:

- the initial clinical presentation of COVID,
- any persistent symptoms other than exercise intolerance,
- clinical characteristics prior to COVID-19 infection (co-morbidities – regular habitual physical activity).

*2.2. Secondary objectives*

- To model the kinetics of ventilatory pattern responses in order to characterize the behavior of excessive hyperventilation and, possibly, chaotic breathing.

- To test, through different statistical models, the possibility of predicting the persistence of dyspnoea as a function of exercise variables, pre-existing clinical data of the COVID, clinical presentation of the acute COVID.

## *3. Investigators and organization of the study*

*3.1. Study data manager*

The study data manager is the association aCCPP represented by its Caretaker President, Vice-President Dr. Philippe Eric Kelkel from the General Hospital Métropolole Savoie.

*3.2. Coordinating investigator and principal investigators of the study*

The principal investigators of the study are:

- Prof. Pierantonio Laveneziana, pulmonologist, Univ. Hospital La Pitié-Salpêtrière, 47-83, bd de l'hôpital, 75651 Paris Cedex 13, FRANCE.
- Prof. Frédéric Costes, pulmonologist, Department of Sports Medicine and Functional Explorations, Gabriel-Montpied Hospital, Univ. Hospital of Clermont-Ferrand. Clermont Auvergne Univ., INRA, UMR 1019, Human Nutrition Unit, Clermont-Ferrand, FRANCE.

The principal coordinating-investigator is Prof. Bernard Aguilaniu, Univ. Grenoble Alpes, FRANCE.

*3.3. Steering committee of the study*

The steering committee is composed of 9 members.

Coordinating investigators:

| | |
|---|---|
| Prof. Bernard Aguilaniu | Univ. Grenoble Alpes, FRANCE |
| Prof. Pierantonio Laveneziana | Univ. Hospital La Pitié-Salpêtrière, Paris, FRANCE |
| Prof. Frédéric Costes | Univ. Hospital of Clermont-Ferrand, FRANCE |

Other members:

Steering committee facilitator: Prof. Bernard Aguilaniu (Univ. Grenoble Alpes, FRANCE)

| | |
|---|---|
| - Dr. David Debeaumont | Univ. Hospital Rouen, FRANCE |
| - Dr. Yan Martinat | Medical Center Parot, Lyon, FRANCE |
| - Dr. Frija-Masson Justine | Univ. Hospital Bichat, Paris, FRANCE |
| - Dr. Motiejunaite Justina | Univ. Hospital Bichat, Paris, FRANCE |
| - Prof. Anestis Antoniadis | IMAG Univ. Grenoble Alpes and Cape Town Univ. SA, FRANCE |
| - Prof. François Péronnet | Univ. of Montréal-Canada, CANADA |

*3.4. Centers and investigators*

The investigators are Pulmonologists, Cardiologists and Physiologists involved in the realization and the diagnostic interpretation of the Cardio Pulmonary Exercise Testing - CPET within public or private structures (Univ. Hospitals, General Hospitals, private practices or mixed).

About 40 investigators are expected.

*3.5. Management center and statistical analysis*

The data management of the study will be carried out by the aCCPP.
A telephone number and an e-mail address will be made available to the participating physicians. The management center will respond to each specific request throughout the study.
Data management is provided by the aCCPP and its contractors.

Statistical analysis will be performed by Prof. Anestis Antoniadis, IMAG Univ. Grenoble Alpes, and Prof. Sophie Lambert Lacroix, MultiDisciplinary Institute in Artificial Intelligence (MIAI) Grenoble Alpes University.

## *4. Design of the the study*

This study is a French-speaking, multi-center, observational, descriptive cohort with retrospective data collection on patients with COVID who present persistent symptoms responsible for intolerance to exercise.

This study does not affect patient management in any way: no additional examinations will be performed, nor will any treatment be administered specifically for this study.

- The (retrospective) data collection will be carried out from July 15, 202 to December 31, 2023 (10 months).
- The data involved cover the period from January 2, 2020 to December 31, 2022 (i.e., 29 months).
- These data were stored by the investigators on-site as part of their usual practice.

The migration of the data collected and stored locally on the CPET-STUDIES.COM platform will take place between February 1, 2022 and May 31, 2023.

*4.1. Constitution of the cohort and data collection*

⇒ From June 1, 2022, pulmonologists, cardiologists and physiologists performing functional exercise tests (CPET), in public or private structures (univ. hospital, general hospital, private practice or mixed) will be officially invited to participate in this study by e-mail.

⇒ Between June 1, 2022 and November 31, 2023, each physician willing to participate in the study will transmit his signed investigator participation form to the management center, and will receive in return the study documents as well as the instructions to implement in their ergospirometer a standardized export file.

⇒ This study will take place over a period of 18 months from June 1, 2022 to December 31, 2023. The data collection concerns patients who had a consultation between January 2, 2020 to December 31, 2022. Therefore, the investigating physicians will identify the files of patients who meet the inclusion criteria of the protocol (§ 5.3), going back to January 2, 2020.

⇒ Once these steps are validated, the investigator will be able to migrate the data (Physiological CPET and Clinical) to the CPET-STUDIES.COM platform, where it will be pseudonymized before any processing.

*4.2. Data migration*
Data migration will be performed on the dedicated CPET-STUDIES.COM platform between February 1, 2023 and December 31, 2023.

## *5. Population of the study*

*5.1. Recruitment procedures*
All patients with exercise intolerance during COVID, diagnosed between January 2, 2020 and December 31, 2022, who have been informed that the physiological data collected during the CPET and the clinical data necessary for its interpretation may be used for clinical research, can be enrolled.

*5.2. Number of Patients*
This study is expected to collect data from approximately 1 000 patients.

*5.3. Eligibility Criteria*
Patients with the following characteristics can be enrolled in this study:
- Age ≥ 18 years
- Patients with persistent symptoms 3 months after the onset of COVID-19 infection, regardless the severity of the initial illness
- Patients with an ICU stay, primarily following rehabilitation management; that is, in practice, at least 6 months after COVID
- Patients followed by a pulmonologist, cardiologist or physiologist in a public or private facility or in private practice, allowing for CPET
- Patients who have performed a CPET before January 1, 2023
- Patients informed of the possible anonymized processing of the data collected during CPET for research purposes; and who gave informed consent

*5.4. Exclusion Criteria*
Patients with the following characteristics will not be enrolled in this study:
- Age < 18 years
- Patients unable to perform CPET for locomotor reasons
- Patients with severely reduced functional work capacity
- Patient deprived of liberty by judicial or administrative decision
- Patients unable to give informed consent

*5.5. Previous and/or concomitant treatments*
As the study is non-interventional, no treatment is prohibited.

## *6. Evaluation criteria*

*6.1. Primary endpoint*
To describe by homogeneous patient subgroups, physiological responses and symptoms during CPET in COVID subjects with persistent symptoms responsible for exercise intolerance.

Homogeneous patient subgroups will consider:
- the initial clinical presentation of COVID,
- any persistent symptoms other than exercise intolerance,
- clinical characteristics prior to COVID-19 (co-morbidities - physical activity level).

*6.2. Secondary endpoints*
- To model the kinetics of ventilatory pattern responses in order to characterize the behavior of excessive hyperventilation and, possibly, chaotic breathing.

- To test, through different statistical models, the possibility of predicting the persistence of dyspnoea as a function of exercise variables, pre-existing clinical data of the COVID, clinical presentation of the acute COVID.

## *7. Procedures of the study*

*7.1. Recruitment of pulmonologists, cardiologists, physiologists and patients*

The recruitment of investigating physicians for this study is based on a voluntary basis.

The list of potential investigating centers corresponds to certain pulmonology, cardiology and physiology departments involved in the realization and diagnostic interpretation of CPET; whether within public or private structures (univ. hospital, general hospital, liberal or mixed activity).

Pulmonologists, cardiologists and physiologists will be invited to participate in the study by an e-mail from the investigating coordinator. An investigator participation form to be completed by the physicians agreeing to participate in the study will be attached to this e-mail. Physicians agreeing to participate in the study will return the completed form to the study management center before November 31, 2003.

All patients meeting the enrollment criteria and having had exercise intolerance during COVID, diagnosed between January 2, 2020 and December 31, 2022, will have been informed that the physiological data collected during the CPET and the clinical data necessary for its interpretation will be possibly exploited for an observational research (see above 5.1. Recruitment procedures).

*7.2. Data collection*

7.2.1. Clinical data

Clinical data recorded (see *Appendix 2*) include:

***Patient***

- Sex, month and year of birth, weight, height,
- Pre-COVID physical activity level (PA): sport (h/week), PA at work, daily PA, time spent sitting,
- Main comorbidities (pulmonary, hypertension, cardiovascular, metabolic, chronic renal pathologies, psychiatric pathologies, cancers),
- Common treatments (therapeutic class) with potential effects on exercise tolerance.

***COVID pathology***

- Date of COVID,
- Severity of initial COVID: oxygen requirement, parenchymal extension on CT-scan, non-respiratory symptoms,
- Post-COVID symptoms: dyspnea, fatigue, cough, muscle and/or joint pain, anxiety, agueusia, anosmia, headache, neurological symptoms, gastrointestinal symptoms, palpitations, dizziness.

***Additional data available***

- Cardiovascular assessment: HR, cardiac ultrasound, MRI,
- Anxiety/depression questionnaire scores and Chalmers fatigue questionnaire,
- Resting respiratory function: $FEV_1$, FVC, SVC, CI, Tlco.
- Helium VA
-

***Symptoms during CPET***

The Borg scale should be used (see *Appendix 3*) for the collection of symptoms during CPET. This scale is used to assess the intensity of breathlessness and muscle fatigue during exercise in patients.

7.2.2. Physiological Data

In order to get rid of some of the variability of the results, the export of physiological data will only concern the measured data. Additional physiological data will then be obtained by applying the appropriate physiological calculation formulas in a strictly identical way whatever the brand of the ergospirometer is. All these data (measured and calculated) will constitute a file called **Finalized File**.

This Standardized file will constitute the physiological source data used to reach the research objectives of the study.

The content of the Standardized file is imported into a database, which contains only the patient's data.

Eventually, the anonymized clinical and exercise physiological (CPET) data will be transferred to a spreadsheet for statistical analysis. In no case will the statisticians have access to the patient's personal information.

*7.3. Data transmission and migration*

A new CPET Open Source Data platform (CPET-STUDIES.COM), designed by HYLAB with the help of the software development company ASCANIO, is intended to collect clinical and physiological data.

The CPET-STUDIES.COM application transforms the files' original data into a Finalized File.

**Access to the platform will be secured** by identification with a login and a password

- The patient's physiological and clinical data will be encrypted and pseudonymized when migrated and/or entered on the CPET-STUDIES.COM platform,
- The content of the Finalized File will then be imported into a database, which contains only the clinical data associated with the patient's pseudonym.

Clinical data:
Pseudonymized data will be stored separately from the rest of the study and will be encrypted. Moreover, for security reasons, data extraction tools will not decrypt these pseudonomyzed data.

Physiological data :
Physiological data in the export file will be migrated to a Finalized File which will, in a homogeneous manner, perform:
- cycle-by-cycle averaging of measured variables over the last 20 and 30 seconds of each minute;
- the calculations required to obtain new variables of interest (called *calculated variables*).

This Finalized File will constitute the SOURCE data for this study, exploitable for the research objectives of the study.

Finally, the anonymized data (clinical and EFX) will be transferred to the R statistical software. Under no circumstances will the statistician have access to the personal information of the patient.

*7.4. Dissemination or publication of the study results*
It is not in the public interest that the results of a study are never made available or considered, especially by public decision-makers or authorized representatives of the community where the study was conducted. Withholding information or refusing to disclose results can only be justified in exceptional circumstances; for example, when methodological problems encountered during the study render the results meaningless. When it is not possible to present or publish all the results or conclusions of an epidemiological study for reasons of limited space or insufficient time to allow such presentation or publication, the person in charge of the study must guarantee that all persons who might be interested in all the results or conclusions will have access to them upon request.
The main results must be communicated to those who participated in the study or their representatives, as well as to other members of the community where the study was carried out In this respect, the scientific committee undertakes to transmit the results of the study to all the investigating physicians who participated in it.

***Intermediate results***
Intermediate results should always be explicitly stated as such. Intermediate results, as well as raw or previously processed data or any data, results, analyses or conclusions that may be derived from these intermediate results, may not be transmitted to third parties or used in other studies unless such transmission or use is explicitly provided for in the protocol and is specifically approved by the study's manager.
In the event that the study is discontinued for any reason, the presentation or publication of any preliminary or partial results or findings from the study may occur subject to compliance with prior validation procedures. Data or results from the discontinued study should be identified as such in subsequent publications and presentations.

***Obligation to publish***
All results of a study, whether the funders are public or private, are the scientific responsibility of the physician in charge of the study, not of the funder, and the results must always be made public if they have sufficient scientific validity.

Any request to hide results, to change or attenuate the content of a report, or to postpone the publication of results, will be categorically rejected.

***Obligation to peer review***
The general rule is to submit the results of a study to an independent peer review before making them public or submitting them to the media.

***Impartiality of publications***
Publications should describe all aspects of the study in an honest and balanced way without taking into account other interests, especially non-scientific ones. Scientific committee members should not exaggerate the results of the study in order to increase their chances of obtaining more funding for future research or to make their articles more attractive to the editor of a journal . A certain bias of selecting results that agree with the view of the physician in charge of the study and ignoring those that contradict it must be avoided. Authors of epidemiological articles must comply with the rules of quality journals in which possible conflicts

of interest are disclosed. The definition and order of authorship should be consistent with scientific publication practices. In this study, the list of investigating physicians will be systematically associated with all publications.

## *8. Statistical analysis*

The source data will be collectively analyzed for subgroup studies defined according to scientific criteria by a committee dedicated to this study.
Analyses will be performed using R software, with all required software packages, and JAGS, in their most up-to-date version at the time of analyses.
No hypotheses will be tested for either the primary or secondary objectives. A descriptive analysis of all evaluation criteria will be performed on the total population and on subgroups to be defined a priori according to the sample.
The variables collected at the end of the steady state, at maximal exercise, and during recovery (Rec + 2') will be expressed as mean, standard deviation (SD), median, quartiles.
Modeling of the kinetics of certain variables (VE-TV-BF-HR) will be performed and then a mathematical model will be developed to quantify and compare these kinetics between subgroups. Comparisons of kinetics between subgroups will be made using recently developed mixed-effects functional analysis of variance (FANOVA) methods.
The kinetics of some variables will be expressed as a function of developed power (in watts), metabolic power ($VO_2$ in L/min), ventilatory flow (in L/min), HR expressed in absolute value, in % of the max HR reached and in % of the predicted value according to the formula maxHR = 210-0.65 x age).

## *9. Sample size*

1 000 patients with exercise intolerance after COVID are expected for the enrollment period.

## *10. Legal and ethical considerations*

*10.1. Ethical considerations*
This study has been filed with the Commission Nationale Informatique et Liberté – CNIL and is registered in the public directory maintained by the French Health Data Hub.

*10.2. Information to patients*
As is commonly done on admission to hospitals, a signed informed consent form will be attached to the administrative and medical file of the patient.

In the absence of an informed consent form, patients who have undergone CPET will be contacted and informed of the modalities of this study in order to sign an informed consent form (*Appendix 1)*.
This will be done as long as it does not involve a disproportionate effort.

*10.3. Pharmacovigilance*
In accordance with the Jardé law, pharmacovigilance reports of serious adverse events (SAEs) concerning drugs will not be collected during the study, nor transmitted to the pharmaceutical companies concerned.
Adverse events and SAEs will be managed by the investigators according to their usual practices.

*10.4. Protocol amendment*
Any modification of the protocol will have to be discussed and approved by the steering committee and will be subject to an amendment.
Minor changes (editorial corrections to improve comprehension, spelling corrections, administrative changes ...) will result in an increase of the number after the dot in the version number: version 1.1 instead of version 1.0.
Major changes will result in an increase of the number before the dot in the version number: version 2.0 instead of version 1.0.
Major changes will be reported to the appropriate authorities.

*10.5. Archiving*
The study data manager, who is also the study management center, will retain all study data for the following periods:

- Patient data: Retention in the controller's information system for up to 2 years after the last publication or, in the absence of publication, until the final research report is signed.
- Professional data: 15 years maximum from the end of the last research in which the health professional participated.

Following this, these data will be archived on paper or computer for a maximum of 20 years in accordance with the Cnil deliberation n° 2018-155 of May 3, 2018 (MR-004).

*10.6. Financial Partner*

This study will be conducted with the financial support of the Pharmaceutical Companies Menarini France and AstraZeneca.

*Appendix 1: Informed Consent Form*

# Informed Consent Form
# June 9, 2023

**Kinetics of physiological and symptomatic responses to CardioPulmonary Exercise Testing (CPET) in subjects with persistent exercise intolerance after COVID-19: an Open-Source Exercise Network**

**Dear Madam, Dear Sir,**

Dr. _____ (LAST NAME, First name), practicing at the hospital/clinic _____,

offers you to participate in a research study to better understand persistent exercise intolerance after COVID. By analyzing information from a large cohort, it is possible to identify subgroups of people with common clinical characteristics that will allow a more detailed understanding of the mechanism and determinants of persistent symptoms, and consequently to propose more adapted treatments.

The physician with whom you have performed a cardiopulmonary exercise test (CPET) is participating in this study which is organized under the aegis of a scientific committee composed of pulmonologists, cardiologists and physiologists.

| | |
|---|---|
| Study data manager: | aCCPP Association 1901<br>**A**ssociation pour la **C**omplémentarité des **C**onnaisances et des **P**ratiques de la **P**neumologie |
| Coordinator: | Pr Bernard Aguilaniu (Grenoble Alpes University Hospital) |
| Principal investigators: | Pr PierAntonio Laveneziana (La Pitié Salpétrière Paris University Hospital)<br>Pr Frédéric Costes (Clermont-Ferrand University Hospital) |

## Information collected - Regulations - Publication

This is an observational study that consists of collecting physiological information from your exercise test and clinical information about your health. This information will be collected on an electronic medium that will allow statistical analysis of all 600 records that we wish to collect. The main data on your health status are:

- Age - weight, height, sex
- History of chronic disease (e.g. cardiovascular, respiratory or metabolic diseases, etc.),
- Date of COVID and initial and persistent symptoms

This observational study, which complies with the French MR-004 reference methodology, is published in the French Health Data Hub national directory. The Declaration of conformity to the reference methodology MR-004 was made to the National Commission for Information Technology and Civil Liberties (CNIL) on April 25, 2022 and bears the reference n°2226149 v 0.

Therefore, your voluntary participation does not require any additional visit or examination compared to your usual care. If you do not want your data to be analyzed, this will not influence in any way the care provided by your doctor. At any time, you may revoke your decision to participate in the study and this decision will not affect your medical follow-up.

All data collected are pseudonymized, i.e., identifying information does not appear at any time in the study documents and publications. They are saved under the responsibility of the aCCPP, promoter of the research.

The aCCPP is responsible for processing your personal data for scientific research purposes in the context of this study (art. 9.2(j) of Regulation (EU) No. 679/2016 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, hereinafter referred to as the "GDPR" or "Regulation"). This processing is implemented on the basis of the legitimate interest of the aCCPP to undertake scientific research in the field of pulmonology (Art. 6.1(f) GDPR).

The data of this research will be kept in the information system of the controller until 2 years after the last publication or in the absence of publication, until the signature of the final report of the research. They will then be archived on paper or digital storage medium for a maximum period of 20 years.

In addition, all research projects carried out by the aCCPP are published on the website: https://colibri.semaphore-sante.fr/. From this site, you can consult the projects in progress, ask questions and also oppose that your personal data contribute to a specific research project. The data collected during this study, aggregated and thus strictly anonymized, will be published in scientific medical journals by the scientific committee. You will be informed of the results through the investigating physician of the medical department in which you are being treated, if you wish, as soon as they are available.

# Rights of data subjects

In accordance with Article 13 of the GDPR, we inform you that your data will be processed in accordance with the Regulation and with the rules of confidentiality to which the aCCPP association attaches particular importance. You have several rights regarding the information about you:

- You can ask to have access to the information concerning you in order to obtain a copy of it and the indication of the uses which are made of it (right of access);
- You can ask to correct and update information about you (right to rectification);
- You may object to the use of this information for research (right to object). This opposition prevents any use or conservation of these data;
- You can obtain the erasure of this data (right to erasure);

You can exercise these rights at any time with the aCCPP, for the attention of the Data Protection Officer (DPO), 19 avenue Marcelin Berthelot, 38 100 Grenoble - FRANCE, dpo@colibri-pneumo.fr, which undertakes to act on them as soon as possible or within a maximum period of one month (article 12.3 of the RGPD). You can also exercise these rights with the doctor who is following you in the study and who alone knows your identity.

- If you consider that the processing of your personal information constitutes a violation of the General Data Protection Regulation, you may lodge a complaint with the CNIL (right to lodge a complaint with a supervisory authority).

# Consent

I freely consent to participate in the study entitled:

**"Kinetics of physiological and symptomatic responses to CardioPulmonary Exercise Testing (CPET) in subjects with persistent exercise intolerance after COVID-19: an Open-Source Exercise Network"**

- I have read the informed consent form explaining the purpose of this study, how it will be conducted and what my participation will entail,
- I have received appropriate answers to all my questions,
- I have understood that my participation is free and that I can interrupt it at any time without incurring any responsibility or any prejudice to the quality of the care I will receive. I will then indicate to the doctor who is treating me whether or not I wish the data collected up to the moment of my decision to be used,
- My consent does not relieve the physician who is following me in the study of any of his responsibilities and I retain all my rights guaranteed by law.

| **Patient's signature** | **Investigating physician's signature** |
|---|---|
| LAST NAME First name : | LAST NAME First name : |
| Date: | Date: |
| Signature: | Signature: |

## *Appendix 2: CPET post-COVID questionnaire*

| *Anonymized Center Code* | ***Anonymized patient code*** | **Sex** | **Age** | **Weight** | **Height** |
|---|---|---|---|---|---|
| ///// | ///// | M/F | years | kg | cm |
| | | | | | |

| **Date COVID** | **Date CPET (EFX)** |
|---|---|
| month/year | day/month/year |

| ***Physical Activity Level before COVID-19*** | | | |
|---|---|---|---|
| *Sport (h/week)* | *Work Activities* | *Daily Physical Activities* | *Seating Time* |
| **No** | **No** | | |
| YES | YES | | < 4 h |
| < 4 h | With movement | Mainly Domestic (Inside) | 4 – 7 h |
| 4-6 h | Without movement | Leisure Time Activities (Outside ≥ 60 min /J) | > 7 h |
| 6 à 10 h | | | |
| > 10 h | | | |
| Sport competition | | | |

| **Main comorbidities** | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Pulmonary Disease* | *Arterial hypertension* | *Cardiac Disease* | *Metabolic Disease* | *Chronic renal failure* | *Chronic Hepatic failure* | *Psychiatric condition* | *Cancer* |
| | | | | | | | |
| **No** | **No** | **No** | **No** | **No** | **No** | **No** | **No** |
| YES | YES | YES | YES | YES | YES | YES | YES |
| Obstructive | | Myocardiopathy | DT2 | | | Anxiety Treated | Cured |
| Interstitial | | Coronary disease | DID | | | Dépression Treated | Remission |
| Vascular | | Valvular disease | Thyroid Insufficiency | | | Psychosis | Progression |
| Others | | Congénital Disease | Others | | | Cognitive disorder | |
| | | Chronic Heart Failure | | | | | |
| | | Others | | | | | |

| **COVID: initial clinical presentation** | | |
|---|---|---|
| Besoin en O2 | CT-scan Parenchyma Extension | Symptomes non respiratoires |
| No | No | No |
| YES | YES | YES |
| 0.5-6 L/min | Mild < 10 % | Prolonged fever |
| > 6 L/min | Moderate 10-24 % | Fatigue |
| Hight Flow | Moderate-to-severe 25-49 % | Joints/muscle pain/stiffness |
| Invasive ventilation | Severe ≥ 50 % | Headache |
| | | Anosmia and/or agueusia |
| | | Gastrointestinal |
| | | Neurological |
| | | Cardiac/Pericardial |

| Symptoms Post COVID | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dyspnoea** | **Fatigue** | **Cough** | **Muscle/ Joint pain** | **Anxiety** | **Agueusie** | **Anosmia** | **Headhache** | **Neurological** | **Gastro intestinal** | **Palpitations** | **Vertigo** | **Others** |
| | | | | | | | | | | | | |
| No | No | No | No | No | No | No | No | No | No | No | No | No |
| Yes | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ | Yes<br>+ /++/ +++ |
| Gasping for breath | | | | | | | | | | | | |
| Shortness of breath | | | | | | | | | | | | |
| Chest tightness | | | | | | | | | | | | |
| Incomplete or unsatisfactory breathing | | | | | | | | | | | | |

| Cardiac Evaluation | | |
|---|---|---|
| ECG | Echocardiography | MRI |
| No | No | No |
| Yes | Yes | Yes |
| Normal | Normal | Normal |
| Abnormal | Abnormal | Abnormal |

| Questionnaires Scores | | |
|---|---|---|
| Hosp. Anxiety and Depression Scale | | Chalmers |
| **Anxiety** | **Depression** | **Fatigue** |
| Not Done | Not Done | Not Done |
| *Value* | *Value* | *Value* |

| Rest Pulmonary Function | | | |
|---|---|---|---|
| **$FEV_1$** | **FVC** | **SVC** | **TICO** |
| (L.) | (L.) | (L.) | (mlco/min/mmHg) |
| *Value* | *Value* | *Value* | *Value* |

| Treatments with potential effects on exercise responses | | |
|---|---|---|
| Pulmonary | Cardiovascular | Others |
| **No** | **No** | **No** |
| Yes | Yes | Yes |
| Bronchodilatators | Betablockers | To be specify |
| | Calcium inhibitors | |

| Maximal Borg Scale | | |
|---|---|---|
| Dyspnoea | Fatigue | Muscular pain |
| 0 to 10 | 0 to 10 | 0 to 10 |

***Appendix 3: Borg scale***

The Borg scale should be used during exercise after giving the following explanation to the patient:

- *This scale will assess the **intensity** of your breathlessness and muscle fatigue during exercise.*
- *I will ask you at regular intervals to indicate **the intensity** of your breathlessness and then immediately afterwards, **the intensity** of your muscular fatigue.*
- *To answer you will have to indicate with your finger the situation that best corresponds to what you feel, either by showing the number from zero to 10, or by indicating the words that best express this intensity.*
- *So I let you read the scale:*
    - *0 corresponds to no breathlessness or fatigue*
    - *10 corresponds to the **maximum intensity** ever felt for breathlessness (or muscular fatigue)*
    - *Right now (at rest), indicate **the intensity** of your breathlessness..., indicate your muscular fatigue*

| **BORG scale** | |
|---|---|
| **0** | Rest |
| **0,5** | Very, Very Easy (barely noticeable) |
| **1** | Very, Very Easy |
| **2** | Easy |
| **3** | Moderate |
| **4** | Somewhat Hard |
| **5** | Hard |
| **6** | |
| **7** | Very Hard |
| **8** | |
| **9** | |
| **10** | Maximal |

***Appendix 4: Methodology of the CPET***

The main recommendations are:

a. No need to record ventilatory measurements in the resting state

b. Continuous recording of ventilatory and ECG measurements; and discontinuous (see below) recording of blood pressure, symptoms and blood gases during the following 3 phases:
   - A steady state phase of 3 minutes at constant load 20-30-40 or 50 watts, depending on clinical situation and body mass.
   - An incremental phase of 10-15 or 20 watts depending on the clinical situation and body mass.
   - A recovery phase for a minimum of 3 minutes without load, pedaling without load.

c. Borg Dyspnea then Borg Muscle Fatigue
   - At the end of the steady state,
   - Every 2 minutes,
   - At maximal exercise,
   - At 3 minutes post exercise (Borg D + Borg F).

c. Capillary or arterial blood gases including lactatemia if possible
   - At the end of steady state,
   - At maximal exercise,
   - Intermediate stages depending on clinical situation

***Appendix 5: HADS questionnaire***

## Hospital Anxiety and Depression Scale (HADS)

**Tick the box beside the reply that is closest to how you have been feeling in the past week.**
**Don't take too long over you replies: your immediate is best.**

| D | A | | D | A | |
|---|---|---|---|---|---|
| | | **I feel tense or 'wound up':** | | | **I feel as if I am slowed down:** |
| | 3 | Most of the time | 3 | | Nearly all the time |
| | 2 | A lot of the time | 2 | | Very often |
| | 1 | From time to time, occasionally | 1 | | Sometimes |
| | 0 | Not at all | 0 | | Not at all |
| | | | | | |
| | | **I still enjoy the things I used to enjoy:** | | | **I get a sort of frightened feeling like 'butterflies' in the stomach:** |
| 0 | | Definitely as much | | 0 | Not at all |
| 1 | | Not quite so much | | 1 | Occasionally |
| 2 | | Only a little | | 2 | Quite Often |
| 3 | | Hardly at all | | 3 | Very Often |
| | | | | | |
| | | **I get a sort of frightened feeling as if something awful is about to happen:** | | | **I have lost interest in my appearance:** |
| | 3 | Very definitely and quite badly | 3 | | Definitely |
| | 2 | Yes, but not too badly | 2 | | I don't take as much care as I should |
| | 1 | A little, but it doesn't worry me | 1 | | I may not take quite as much care |
| | 0 | Not at all | 0 | | I take just as much care as ever |
| | | | | | |
| | | **I can laugh and see the funny side of things:** | | | **I feel restless as I have to be on the move:** |
| 0 | | As much as I always could | | 3 | Very much indeed |
| 1 | | Not quite so much now | | 2 | Quite a lot |
| 2 | | Definitely not so much now | | 1 | Not very much |
| 3 | | Not at all | | 0 | Not at all |
| | | **Worrying thoughts go through my mind:** | | | **I look forward with enjoyment to things:** |
| | 3 | A great deal of the time | 0 | | As much as I ever did |
| | 2 | A lot of the time | 1 | | Rather less than I used to |
| | 1 | From time to time, but not too often | 2 | | Definitely less than I used to |
| | 0 | Only occasionally | 3 | | Hardly at all |
| | | | | | |
| | | **I feel cheerful:** | | | **I get sudden feelings of panic:** |
| 3 | | Not at all | | 3 | Very often indeed |
| 2 | | Not often | | 2 | Quite often |
| 1 | | Sometimes | | 1 | Not very often |
| 0 | | Most of the time | | 0 | Not at all |
| | | | | | |
| | | **I can sit at ease and feel relaxed:** | | | **I can enjoy a good book or radio or TV program:** |
| | 0 | Definitely | 0 | | Often |
| | 1 | Usually | 1 | | Sometimes |
| | 2 | Not Often | 2 | | Not often |
| | 3 | Not at all | 3 | | Very seldom |

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____

***Appendix 6: Chalder faigue scale***

**Completion of the Chalder fatigue scale**

**Explanation to be given:**

"Indicate for each question how you are currently doing compared to your status before COVID infection"

| | Less than usual | No more than usual | More than usual | Much more than usual |
|---|---|---|---|---|
| **PHYSICAL SYMPTOMS** | | | | |
| 1. Do you have problems with tiredness? | | | | |
| 2. Do you need to rest more? | | | | |
| 3. Do you feel sleepy or drowsy? | | | | |
| 4. Do you have problems starting things? | | | | |
| 5. Do you lack energy? | | | | |
| 6. Do you have less strenght in your muscles? | | | | |
| 7. Do you feel week? | | | | |
| **MENTAL SYMPTOMS** | | | | |
| 8. Do you have difficulties concentrating? | | | | |
| 8. Do you make slips of the tongue when speaking? | | | | |
| 8. Do you find it difficult to find the right word? | | | | |
| 8. Do you have memory difficulties? | | | | |

**Scoring of responses**

Less than usual = 0 No more than usual = 1
More than usual = 2 Much more than usual = 3

**2 Possible scores:**

⇒ Total of the 11 questions: ≤ 11/33 = no difference / before COVID

⇒ Answers YES/NO Every response 0 or 1 = 0 (so the 2 left colums)
Every response 2 or 3 = 1 (so the 2 right colums)
Increased fatigue (YES) if the sum of the 2 right columns is > 4

*Craig Jackson. The Chalder Fatigue Scale (CFQ11) Occupational Medecine 2015*