



ENERGY

The Ean NEuro-covid ReGistrY Consortium

Version 01

October 2020

Core Scientific Committee

Claudio Bassetti, Neurology Department, University Hospital, 3010 Bern, Switzerland

Ettore Beghi, Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Raimund Helbok, Department of Neurology, Neurocritical Care Unit, Innsbruck, Austria

Elena Moro, Division of Neurology, Centre Hospitalier Universitaire, Grenoble, France

Pille Taba, Neurology Clinic of Tartu - University Hospital

Michael Crean. Press & Communication, European Academy of Neurology, Vienna, Austria

Advisory Committee

All members of the EAN Covid-19 Task Force

Enlarged Scientific Committee

Two representatives from Italy, Spain and Portugal; one representative from any other participating country.

Data Management

Lalit Kaltenbach, Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Austria

Giorgia Giussani, Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

Statistical analysis

Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Austria

Elisa Bianchi, Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

Table of Changes

Date	Page/Section	Description of Change
July 29	Pg. 6 / procedure section	Sentence added which allows for inclusion of retrospective patient data
September 7	Pg. ... Pg. ... Pg. ...	<p>Secondary objectives: Added "... and non-European countries"</p> <p>Methodology: "Included will be all COVID-19 patients whom the neurologists have been asked to visit or are available in the local registries and fulfilled the inclusion criteria. Both retrospective and prospective cases are eligible for inclusion."</p> <p>CRF: Added "Final COVID-19 status"</p>
September 19	Pg. 8	Information on data sharing with third countries.

Background & Rationale

An unexpected outbreak caused by COVID-19 virus is devastating the world population and the global economy. Europe is at present the continent with the highest number of affected individuals and deaths. Despite the exponential increase in the number of infections, information available on the full spectrum of the disease is still insufficient. Recent reports strongly suggest that COVID-19 infection spreads to organs other than the respiratory system, including the central and peripheral nervous system. The involvement of the nervous system can be due to a direct action of the virus on the nervous tissue and/or to an indirect action through the activation of immune-mediated mechanisms. Moreover, the need for prolonged intensive care management in severe COVID-19 patients leads to well-known adverse effects on the central and peripheral nervous system, including post Intensive Care Unit (ICU) syndrome and ICU acquired weakness.

At present, information available on the involvement of the nervous system during this outbreak is based on case reports and retrospective clinical series. These sources are open to selection bias, although there are indicators that neurological complications in COVID-19 patients are associated with a worse outcome. In addition, both differences in the dissemination of the infection across Europe and variability of measures adopted to contrast the outbreak prevent a correct surveillance of the clinical characteristics of the infection, including the occurrence of neurological disorders.

Currently available information can provide a picture of the rich spectrum of symptoms, signs, and diagnoses associated with COVID-19 infection. However, in the light of the wide differences in timing and severity of the outbreak across Europe, it is impossible to define the association between the impairment of neurological functions and the outcome of the infection. Consequently, to adopt adequate preventing measures without a systematic collection of the information in a well-defined cohort of patients is very challenging. Only a registry can shed some light on the burden and general characteristics of neurological complications of the COVID-19 outbreak and the association of these complications with the demographic and clinical features of the affected individuals.

Objectives

The main objective of this international Registry is to provide epidemiological data on neurological manifestations (symptoms/signs and diagnoses) in patients with COVID-19 infection reported by neurologists in outpatient services, emergency rooms, and hospital departments. The EAN registry can be implemented as *stand-alone* registry for COVID-19 patients or as *an addendum* to an existing registry not targeting neurologic signs and symptoms.

1. **Primary objectives** are:
 - a. To evaluate the prevalence of neurological manifestations in patients with *confirmed* COVID-19 disease
 - b. To assess the general characteristics of the neurological manifestations.
2. **Secondary objectives** are:
 - a. To collect epidemiologic data on neurological manifestations of the COVID-19 infection in European and non-European countries
 - b. To evaluate the prevalence of neurological manifestations in patients with suspected COVID-19 disease
 - c. To study the outcome of neurological manifestations in COVID-19 patients (including the incidence of new neurological manifestations)
 - d. To evaluate the incidence of neurological manifestations during follow-up.

Working hypotheses

1. Neurological manifestations are relatively common in COVID-19 patients
2. There may be variability in neurological manifestations among different countries
3. Neurological manifestations and complications contribute to worse outcome in confirmed COVID-19 patients.

Promoter

The Registry is promoted and endorsed by the European Academy of Neurology (EAN).

Participants to the Registry

National Neurological Societies or divisions of Neurology from individual academic centres can apply to participate to the ENERGY Consortium.

Study design

Methodology

Neurologists are asked to implement this study protocol in their institution/clinic, to assess and record demographic and other data, neurologic symptoms and signs according to the annexed electronic Case Record Form (eCRF) in confirmed and suspected COVID-19 patients. Included will be all COVID-19 patients whom the neurologists have been asked to visit or are available in the local registries and fulfilled the inclusion criteria. Both retrospective and prospective cases are eligible for inclusion.

The minimum requirement is to register COVID-19 patients with neurological symptoms and/or signs and/or defined neurological disorders (see inclusion criteria). However, the inclusion of ALL patients with confirmed COVID-19 infection is encouraged to provide the numbers for the calculation of the fraction of the affected population attributable to neurological disorders and the comparison of the overall spectrum of the disease in people with and without neurological manifestations. In centres accepting to include all COVID-19 patients, another physician may be assigned as the person in charge of registration.

Patients

Inclusion criteria

For all COVID-19 patients

- Age 18 or older
- Symptoms suggesting COVID-19 infection OR confirmed COVID-19 infection
- Provided informed consent (according to the requirements of local regulatory agencies).

For COVID-19 patients with neurological signs, symptoms and/or defined neurological disorders

- Age 18 or older
- Symptoms suggesting COVID-19 infection OR confirmed COVID-19 infection
- Neurological evaluation/consultation

- Provided informed consent (according to the requirements of local regulatory agencies).

Exclusion criteria

- Symptoms suggesting other (pulmonary/systemic) infection than COVID-19 AND other confirmed infection.

Procedure

Patients' inclusion can be performed prospectively, at the time of the visit or at patient's discharge, whichever is most convenient; or retrospectively, provided that all inclusion criteria are satisfied. Visits can be performed anywhere in the context of health care facilities (outpatient services, emergency rooms, hospital departments). If at the time of the visit, the clinical picture of the patient is incomplete, the neurologist is invited to contact the caring physician upon discharge to complete the e-CRF. The collection of the data will be kept to a minimum to prevent attrition and loss of data due to the constraints posed by the outbreak. No additional investigations are needed besides a detailed neurological examination and common variables recorded in this pandemic. The registration of the patients will continue until the end of the outbreak.

All registered patients with neurological symptoms will be followed up to 12 months, with telephone calls at 6 and 12 months, to verify clinical conditions, functional abilities, and identify neurological manifestations that might have occurred after the acute phase of the disease. The neurologist (or a designated partner of the local study team) will oversee the follow-up.

A guide is annexed to this protocol to define each variable and facilitate data collection in the e-CRF.

Statistical analysis plan

Descriptive statistics will be performed on all variables collected in the registry. Inferential statistics will include univariate and multivariate analyses. Cross-tabulations will be performed for each symptom, sign and neurological diagnosis against demographics and the other clinical variables, including comorbidities and the main complications of infection. These data will be presented in the entire sample and for each country separately. The neurological diagnoses made at the time of the infection will be contrasted to the status at last observation (recovered, alive with functional impairment, dead). The prevalence of neurological symptoms, signs and diagnoses will be calculated using the number of neurological consultations as denominator and symptoms/signs and, separately, neurological diagnoses as a group. Multivariate analyses will be also performed using logistic regression models with status at last observation (alive with or without functional impairment/dead) as the dependent variable and neurological diagnoses as the independent variables, adjusting for demographics, comorbidities, centre and country. Follow-up data will be analysed in survivors with Kaplan-Meier curves using the occurrence of a neurological diagnosis as the outcome variable and demographics and comorbidities as prognostic predictors. Comparisons will be tested with Log-rank and independent prognostic predictors will be assessed using Cox's hazard models, adjusting for centre and country. The significance will be set at the 5% level ($p=0.05$).

Sample size calculation. The primary endpoints of this registry are to determine the prevalence and the general characteristics of neurological manifestations in COVID 19 patients. The hypotheses of this registry are exploratory; hence a sample size calculation has not been performed.

Benefit and risk ratio

ENERGY will not interfere with the diagnostic and therapeutic decisions made by the attending physicians for the management of the disease. There may be a benefit for patients undergoing neurological examination by early identification of neurological symptoms and signs which may result in a specific treatment. Therefore, the detection of complications may lead to a better management of patients included in this registry.

Consecutive data collection will result in a better understanding of neurological disease manifestations and complications in suspected and confirmed COVID-19 positive patients. This will be important for an early identification of core neurological symptoms during the pandemic.

Collection of data

Routinely captured data will be collected in a web-based eCRF (REDCap) and stored in a password-protected database not accessible directly from the internet. The password is provided to every participating site. Each centre will be assigned a numeric code generated by the central database. The data will be securely stored at the Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Austria contracted by the EAN central office. All procedures will comply with the EU Regulation 2016/679 (DSGVO, *engl.* GDPR) on the protection of natural persons regarding personal data processing and movement.

Ethical standards

The Principal Investigators (PIs) will ensure that the study is conducted in full conformity with the Declaration of Helsinki and Good Clinical Practices.

Ethics committee

The protocol will be submitted by the PI to the local ethics committees (ECs). Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the survey. Only individual data collected after the patient's informed consent will be used. Every eligible patient will be assigned an anonymized code.

Data confidentiality

Participants' and centres' confidentiality is strictly held in trust by the participating investigators. All medical or administrative staff with an access to the data is subject to a duty of confidentiality and data protection. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidentiality agreement protocols.

The study sponsor (European Academy of Neurology) and representatives of local authorities may inspect all documents and records required to be maintained by the local investigator for the participants in this registry. Research data of the registry, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Data Managers and the Statisticians of the registry. For this purpose, data will be de-identified and anonymized at input into the eCRF by the local centres/PIs. Individual participants and their research data will be identified by a unique identification number. The eCRF system used by clinical sites and by research staff will be secured and password protected. In the situation when a centre would be temporary not able to access the

eCRF or complete it, a paper-based CRF will be available on demand. To keep administration and data correctness on a high level, this possibility should only rarely be used. These records will be entered in the eCRF at the EAN central office in collaboration with the research staff of the Medical University of Innsbruck and the Mario Negri Institute of Milan.

Data sharing & ownership

Where ENERGY is an addendum to other registries or databases, formal collaborations can be activated with European and international organisations to share common variables in the intent to provide a broad European and even worldwide picture and favour comparisons. For countries with independent registries/databases and that wish to share their data but are unwilling to use this registry, data will be compared in aggregate using pre-specified statistical plans. The data collected by individual centres will be accessible to these centres without restriction. All participants should be registered as active members of the EAN Neuro-COVID Registry Consortium.

The data collected can be also used to test scientific hypotheses forwarded by any active member. However, these hypotheses should be illustrated in ad-hoc protocols to be submitted for approval to the Registry Core Scientific Committee. The scientific reports should be published on behalf of the EAN and the affiliated neurological societies.

Participating sites will be informed of any data sharing agreement with organisations in countries not associated to the European Union.

Publication, and Authorship

Data will be made available to the scientific community by means of abstract or scientific papers submitted to peer-reviewed journals. Authorship of the main manuscript will follow the ICMJE recommendations that base authorship on the following four criteria:

- Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, AND
- Drafting the work or revising it critically for important intellectual content, AND
- Final approval of the version to be published, AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A writing committee composed by the Core Scientific Committee will draft the work and will be authors of the manuscript. All publications will be made in the name of ENERGY Consortium. All those who satisfy the criteria for authorship will be listed as authors. Each centre will be mentioned at least by the name of one author and listed "on behalf of the ENERGY consortium" in the main publications in PubMed. Additional authors will be listed based on the contribution of each site to the registry. Each author's contribution within the Consortium will be specified.

Case Record Form

Centre ID

Patient's code

Site of visit

- Hospital
- Emergency room
- Outpatient service
- Other (spec)

Year of birth

Sex

Height

Weight

Smoking (no/yes)

Source of contagion

- Occupation
- Family member
- Social
- Travel
- Other (specify)

Date of first symptoms of infection

Final COVID-19 status

Comorbidities in history (no/yes)

If yes, check all that apply

- Arterial hypertension
- Diabetes
- Cardiovascular disease
- Chronic kidney disease
- Chronic liver disease
- Chronic bronchial/pulmonary disease
- Anemia
- Cancer
- Immune-mediated disease
- Other non-neurological (specify)

Neurological disease Premorbid Modified Rankin Scale

Relevant COVID-19 complications (not present in history) (No/Yes)

If yes, check all that apply

- Dyspnea
- Pneumonia
- Cardiovascular disease
- Renal insufficiency/dialysis
- Coagulation disorder/disseminated intravascular coagulopathy
- Septic shock
- Extracorporeal membrane oxygenation
- Other (specify)

Hospital admission (no/yes)

ICU admission (no/yes)

Mechanical ventilation (No/Yes)

New neurological symptoms/signs/diagnoses (no/yes)

If yes:

Date of onset of neurological symptoms/signs

Check all that apply and state if related/unrelated to COVID-19

- Headache
- Hyposmia/hypogeusia
- Dysautonomia
- Vertigo
- Myalgia
- Sleep disturbances
- Excessive daytime sleepiness/hypersomnia
- Cognitive impairment
- Dysexecutive syndrome
- Hyperactive delirium
- Hypoactive delirium/acute encephalopathy
- Stupor/coma
- Syncope
- Seizures/status epilepticus
- Meningitis/Encephalitis
- Stroke
- Movement disorders
- Ataxia

- Spinal cord disorder
- Peripheral neuropathy
- Other (specify)

Diagnostic tests

- CSF (No/Yes)
- CT/MRI (No/Yes)

Outcome

- Modified Rankin Scale at discharge
- If patient died, date of death
- If death, autopsy (No/Yes)

Follow-up

6 months

- Modified Rankin Scale
- Occurrence of new neurological issues (No/Yes)
- If yes, date of onset and specification
- If patient died, date of death
- If death, autopsy (No/Yes)

12 months

- Modified Rankin Scale
- Occurrence of new neurological issues (No/Yes)
- If yes, date of onset and specification
- If patient died, date of death
- If death, autopsy (No/Yes)