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Study Protocol

LEOSS

Lean European Open Survey on
SARS-CoV-2



&



ESCMID Emerging Infections Task Force (EITaF)

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2. PROTOCOL SUMMARY

Title	Lean European Open Survey on SARS-CoV-2 (LEOSS): An Prospective Observational Study
Primary Objective(s)	To identify independent predictors of outcome in patients with diagnosed infection by SARS-CoV-2.
Study Design	Lean European Open Survey on SARS-CoV-2 (LEOSS) is a European non-interventional prospective cohort study in order to overcome the lack of knowledge about epidemiology and clinical course of SARS-COV-2 to further develop evidence-based diagnostic and therapeutic recommendations. Data collection will be performed retrospectively after a patient case has been completed (treatment is finished or patients death). Recruitment will be bidirectional, including past patients, and prospective identification of patients with confirmed SARS-CoV-2 diagnosis. Only data from standard of care treatment will be collected (secondary data use).
Study Population	<ul style="list-style-type: none"> • Patients with confirmed SARS-CoV-2 (PCR – confirmed) • Patients who were diagnosed or received treatment in one of the member states of the EU/EEA
Study Duration	Starting March 2020. Open end, as the course of the SARS-CoV-2 pandemic is not yet foreseeable.
Statistical Methods	<p>This study group will present a descriptive statistic about included cases, sociodemographic characteristics, and clinical course on a daily/weekly base. Correlation with specific treatment strategies will be analyzed by using Chi-square or Mann-Whitney test and regression analysis as appropriate. Time to event analysis, by using Kaplan-Meier and Cox proportional hazard models, will be performed to examine factors associated with the clinical course of SARS-CoV-2.</p> <p>The latest statistics as well will be publicly available on https://www.leoss.net. An anonymised data set will be available to the cooperation partners, protected by a password. Since the anonymous dataset is released to the research community, it will not be possible to maintain control on analyses performed by international researchers.</p>

3. BACKGROUND

In December 2019, a novel coronavirus, entitled as Severe Acute Respiratory Syndrome Coronavirus II (SARS-CoV-2), emerged in Wuhan, China and spread rapidly worldwide. SARS-CoV-2 causes respiratory illness and can spread from person to person [1, 2]. SARS-CoV-2 was declared as a public health emergency of international concern by the end of January 2020. On 8 March 2020, SARS-CoV-2 is affecting 111 countries and territories with 111,817 confirmed cases worldwide, including 3,893 fatalities. In the European Union (EU) (including the Member states of the European Economic Area (EEA) and the United Kingdom), 9,161 cases, including 251 fatalities have been reported in 27 countries [3], with daily rising numbers.

The WHO aggregated preliminary knowledge about the outbreak, transmission dynamics and clinical symptoms in a recent report but stresses the necessity for more in-depth research [4]. Importantly, many knowledge gaps remain regarding best possible clinical management of patients with the infection as well as prediction and prevention of severe outcomes.

In order to record confirmed European SARS-CoV-2 cases uniformly and to establish an evidence base for best practice in clinical management, analyses of a comprehensive SARS-CoV-2 cohort is required and mandated by the SARS-CoV-2 Emerging Infections Task Force (EITaF) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the German Society of Infectious Diseases.

4. OBJECTIVES

4.1. PRIMARY OBJECTIVE

To identify independent predictors of outcome in patients with diagnosed infection by SARS-CoV-2.

4.2. SECONDARY OBJECTIVES

EPIDEMIOLOGY & HEALTH ECONOMICS

- To assess the incidence of complicated and critical infection by SARS-CoV-2
- To assess potential risk factors of complicated and critical infection by SARS-CoV-2
 - Multivariable hazard models including all documented risk factors based on existing literature and stepwise backward or enter method to identify the best model that explains the data
- To assess clinical and sociodemographic characteristics of patients with SARS-CoV-2 infection (descriptive)
- Assessment of the temporal relationship between the severity of SARS-CoV-2 infection and death
 - Multivariable hazard models with time-varying covariates
- Assessment of regional differences in management and clinical outcome (descriptive)
- Monitoring different trends over time (symptoms, incidence) (descriptive)
- Estimation of direct health care costs based on length of stay, time on ICU, time with mechanical ventilation, time on ECMO (descriptive)
- Cost utilization based on coded DRG and reimbursement (descriptive)
- Assessment of the relationship between SARS-CoV-2 and the health economic burden in terms of direct treatment costs incurred during hospitalization (descriptive)

CLINICAL COURSE

- To describe the clinical pattern of disease:
 - Sequence and reversibility of symptoms (descriptive)
 - Sequence of radiographic imaging findings (descriptive)
 - Sequence of laboratory lab results and patterns of disease severity (descriptive, multivariable binary logistic regression model)
 - Sequence of virus detection and quantity in various bodily fluids and samples (descriptive)
 - Immunological / inflammatory features of severe infection (descriptive, multivariable binary logistic regression model)

- Influence of clinical management, including medication, ventilation, supportive care, and monitoring, on outcome and disease duration (multivariable hazard model with time-varying covariates)

5. METHODOLOGY

5.1. STUDY DESIGN

Lean European Open Survey on SARS-CoV-2 (LEOSS) is a prospective European multi-center cohort study in order to overcome the lack of knowledge about epidemiology and clinical course of SARS-CoV-2. The study will allow retrospective inclusion of patients treated before initiation of the study. Patients will be documented anonymously.

5.2. STUDY PERIOD

Start date: As soon as possible after March 16th, 2020

End date: Currently open end, as the course of the pandemic is not foreseeable. If no amendment is filed, the study will be concluded by Dec 31st, 2021

5.3. STUDY POPULATION

For this cohort study, there is no defined upper limit to the number of patients to be recruited. Higher patient numbers will help improving prognostic models and pattern recognition. The board of investigators will make the decision, when additional cases are no longer likely to improve understanding of the disease.

INCLUSION CRITERIA

- Patients with confirmed SARS-CoV-2 infection by PCR diagnosis from nasopharynx, oropharynx, stool, or blood. Rapid tests are an acceptable alternative.

EXCLUSION CRITERIA

- The study will be governed, announced, and disseminated via ESCMID and other channels across Europe. However, treatment in another country is not a formal exclusion criterion.

5.4. DATA COLLECTION

The data collection should be performed retrospectively after a patient case has been completed (treatment is finished or patient's death). This process will be compliant with all applicable European and German federal data protection regulations, including EU directive 2016/679 and the German DS-GVO. The electronic case report form (eCRF) will be provided using the ClinicalSurveys.net online platform of the University Hospital of Cologne (UHC). ClinicalSurveys.net is hosted by QuestBack, Oslo, Norway on servers in Cologne, Germany as part of a software-as-a-service agreement. The proprietary software allows rapid design and deployment of eCRFs. Investigators from participating study sites log into the system with username and a safe password including letters, numbers, and symbols. All investigators can only view and modify their own contributions. All data transmissions are encrypted via TLS

1.2 with an AES 256 GCM bit key and ECDHE RSA key exchange; certificate provided by COMODO RSA Domain Validation Server. Data is documented anonymously; no directly identifying data are stored on QuestBack servers. Regular data-backup, hierarchic management of rights and authentication protocols ensure the protection of data from unauthorized access and loss. All Good Epidemiological Practice (GEP) requirements are met by the software [5].

Administration of the eCRF is limited to selected and named administrators at UHC, who receive comprehensive training in the system before access is granted. Secure passwords are also enforced for administrators and they have to regularly change their passwords. Any data manipulation by users and administrators is logged in an audit trail allowing complete data reconstruction. Server administration is performed by QuestBack, and includes regular updates of the linux-based servers, rigid firewall configuration, current virus and threat detection, and daily backups (on-site and off-site with secure storage).

Contracts between UHC and QuestBack regulate ownership and responsibility for data and eCRFs. Regular on-site audits of security and data protection measures are performed at QuestBack Cologne by UHC. The platform has been extensively used in numerous surveys and studies and has received approval by the responsible data protection officers at UHC.

An abstraction manual will be developed as a companion to the eCRF and will be integrated as automated guidance for the abstractor.

The eCRF will be accessible through <https://www.clinicalsurveys.net>.

The study protocol, the full eCRF as portable document file, and the ethics committee's approval of the study will be available on this site. Partner sites wishing to contribute cases will receive account-details for login. Account details have to be requested via E-mail. Full name, institution and E-mail address have to be supplied. Since the study at hand is specifically at risk for trolling and fake information, we will log IPs and providers and check for plausibility of locator results and supposed background of the participating investigator. Investigators will be informed about handling of their personal data and their IP and location during the registration process.

5.5. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

Data documentation should be performed retrospectively after treatment is finished or patient's death. Documentation will be strictly anonymous. The eCRF will ensure the documentation of the following items (for further details on visit schedule, aggregation, and categorization, see **Appendix A**):

- Age category, gender, ethnicity
- Country of origin, country of diagnosis, ethnicity, first 3 digits of ZIP code
- Month of first positive test
- Assumed time of contracting infection

- If available: L or S Strain
- Observed stages of disease (see above, uncomplicated phase, complicated phase, critical phase, recovery phase), each with time to event
- Overall days of observed follow-up
- Status at last follow-up (survival, severity, virus detection)
- Baseline values (each in five categories of severity) of:
 - GOT/AST, GPT/ALT, GGT, bilirubine, creatine, lipase, leukocytes, lymphocytes, platelets, troponin, CRP, IL-6, PCT, ferritin, IL-2, LDH, d-dimers
 - SO₂, RR, pulse, paO₂, paCO₂
- Important comorbidities
- Smoker, pack years in four categories
- Duration of (i) symptomatic phase, inpatient stay, ICU stay, mechanical ventilation
- Coded DRG
- Patient provided informed consent for scientific use of her or his data?*
- Biomaterial samples available?*
- Symptoms of complicated disease
- Type of viral diagnostics
- Sample location of primary diagnosis
- Highest recorded viral loads / lowest PCR cycles
- Anti-SARS-CoV-2 antibody titer
- Imaging with results (5 categories)
- Therapeutic measures (only yes/no):
 - Antivirals
 - Antibacterial prophylaxis (Betalactams, macrolides, fluoroquinolones, others)
 - Steroids
 - Immunoglobulines
 - ACE inhibitors
 - Betablockers and/or anti-arrhythmics
 - Tocilizumab
 - Plasmapheresis
 - Catecholamines (with duration in days)
 - Invasive / non-invasive mechanical ventilation (with duration in days)
 - ECMO and comparable procedures (with duration in days)
 - Cardiac assist device
 - Others
- Concomitant medication (only yes/no)
 - ACE inhibitor
 - Statines
 - Steroids
 - CNI / mTor inhibitor
 - Anti-TNF-alpha
 - Other immunosuppression

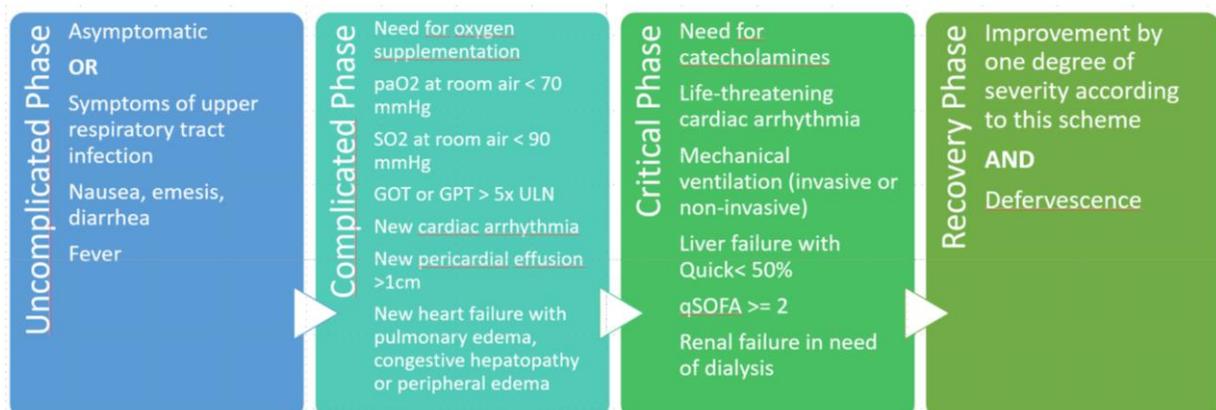
- Chemotherapy
- First values (in five categories) after intubation of:
 - SO₂, RR, Puls, PaO₂, PaCO₂
 - PEEP, Pmax, frequency, FiO₂
- Worst values (in five categories) of:
 - GOT/AST, GPT/ALT, GGT, bilirubine, creatine, lipase, leukocytes, lymphocytes, platelets, troponin, CRP, IL-6, PCT, ferritin, IL-2, LDH, d-dimers
 - SOFA
 - SO₂, RR, pulse, paO₂, paCO₂
 - PEEP, Pmax, frequency, FiO₂
- Proven super-infection (bacterial, fungal)

*) For clarity, note that data will not be stored with a pseudonym and that published data will not contain the documenting investigator. Researchers looking for additional data or biomaterial will only be able to contact the data management and let them know they are looking for patients with defined features that provided biomaterial and/or informed consent. The data management can now inform investigators who have at least one fitting patient that there is a certain request they may want to answer or not, without the ability to point out a specific patient.

5.6. DEFINITIONS

All data capture will be aggregated over five meaningful clinical phases: baseline, uncomplicated phase, complicated phase, critical phase, and recovery phase. It was decided not to rely on the criteria of serious and critical disease from the WHO reports, since e.g. cardiac complications seem to be causative for part of the mortality and are not part of these criteria.

Figure 1: Stages of Disease



5.7. STATISTICAL ANALYSIS

All statistical analyses will be performed using STATA, Python, and/or R statistic software and will be performed by trained personnel (epidemiologist, statistician, health economist) using current methods of analysis.

In general, we will ensure the best possible data quality by plausibility and completeness checks at the time of data entry and by central monitoring of the data records. To counteract possible data manipulation, the documented cases will be checked with regard to the IP address and the documenting center.

We will present a descriptive statistic about included cases, sociodemographic characteristics, and clinical course on a daily/weekly base. Correlation with specific treatment strategies, patterns of disease severity, and lab results will be analyzed by using Chi-square test or Mann-Whitney test as appropriate. In order to assess potential risk factors of complicated and critical infections by SARS-CoV-2 uni- and multivariable regression models will be performed, including all documented risk factors based on existing literature and using stepwise backward or enter method to identify the best model. Time to event analysis, will be performed by using Kaplan-Meier and Cox proportional hazard models, considering time-varying covariates, to examine factors associated with the clinical course (including death) of SARS-CoV-2.

The latest statistics will be publicly available on <https://www.leoss.net>. An anonymised data set will be made available to the cooperation partners in a password-protected manner. A customized version of the anonymized data set (e.g. statistics on cases in your region, cases in your hospital) will also be available to all cooperating centers.

Since the data will be available to the research community for further investigation, it is not possible to foresee further ways of analysis. We will inform through our site that secondary analyses may warrant IRB approval based on local laws and regulation. Regarding protection of anonymity, see section 7 below.

6. BUDGETARY INFORMATION

This study has been created and organized by the protocol writing committee during scientific work hours, evenings, and weekends, to gather clinical knowledge for the sake of current and emerging patients of the 2020 pandemic. There was no dedicated funding for the study and no funds can be made available for documentation. The protocol writing committee states to have no applicable conflict of interest with any of the interventions, devices, or drugs that may or may not be documented by participating investigators in their patient care.

7. ETHICAL AND REGULATORY CONSIDERATIONS

We will submit the final protocol to the ethics committees of the University Hospital of Cologne and Frankfurt (Germany) and – where necessary – to other ethics committees and institutional review boards at other partner sites. While not primary goal of this study, since statistics could result in conclusions being made on various management strategies, including use of pharmaceutical drugs or medical devices, we will register LEOSS as an observational study (“Anwendungsbeobachtung”) according to §67 (6) of German drug law. All study procedures are liable to Good Epidemiological Practice requirements as well as German and European legislation. Where applicable, the investigators will uphold and guarantee the standards of Good Clinical Practice in their conduct. No study interventions will take place throughout this study.

7.1. PRIVACY CONSIDERATIONS

Comprehensive measures will be taken to rule out risk of reidentification for patients registered in the study without written informed consent:

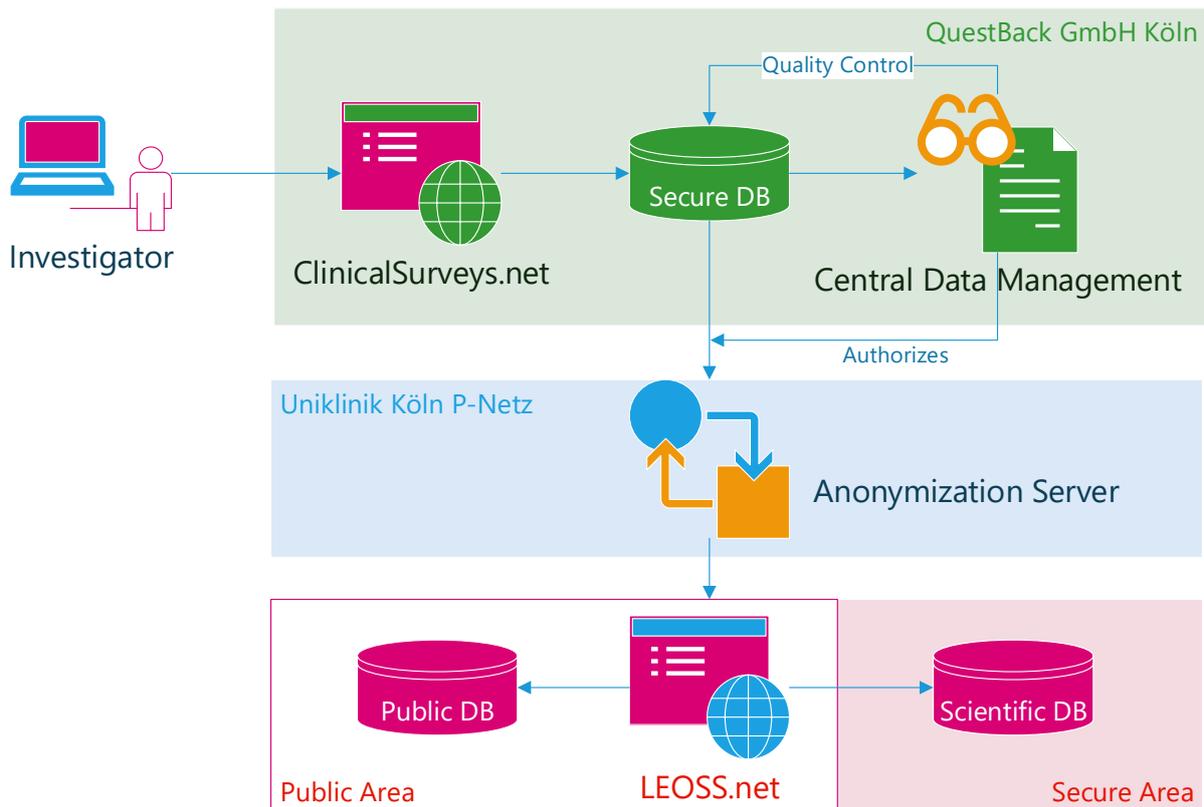
- The data set of LEOSS does not contain any directly identifying information, i.e. no name, birth date, place of living, insurance company or any identifiers linked to the patient record or any other file at the participating center.
- We will not ask for any specific dates. Day of diagnosis will remain unknown to the study, only the month will be specified. All major events will be recorded as days from diagnosis, almost all data will be aggregated over major stages of the infection.
- Almost all data will be asked in categories, e.g. age groups, lab values etc., making a reverse database search in the hospital information system almost impossible.
- All text items will be screened for potentially identifying information. Accidental breaches of anonymity will be reported to the responsible investigator and permanently deleted from the database. Relevant and shareable information will be moved into a structured data item.

While the full data set will be maintained in the protected system of ClinicalSurveys.net (Secure DB), we intend to regularly publish the available data for shared analysis. Since this will deliberately expose documented data to large group of people, additional steps will be taken to further reduce remote risks of reidentification:

- Each data item will be checked individually for the number of cases with a given category. All categories that have been selected less than 10 times will be summarized in a “locked” category until more data becomes available.
- All text items will be dropped before publication.
- Numerous additional items not immediately needed for health-related outcomes, e.g. DRG, will also be dropped.

- The remaining dataset will be the “Scientific DB” and stored in locked area of <https://leoss.net>, where it can only be accessed by invited and accredited investigators.
- For general overview of the study progress and to inform public health representatives, a “Public DB” will also be created with some core information on the dataset. The Public DB will be available to download for everyone on <https://leoss.net>.

Figure 2: Data Security & Workflow



To avoid any ambiguity, the collected dataset in the Secure DB will be considered anonymous by all applicable standards. The “Anonymization Server” performs a second layer of anonymization and double checks that no single data point stands out in the early phase of recruitment, thus regrouping and aggregating data before publication.

7.2. PARTICIPATING CENTERS AND GOVERNANCE:

All centers caring for patients with SARS-CoV-2 infection will be invited to participate in this study. A preliminary list of collaborating institutes and scientific collaboration partners are listed in **Appendix B**.

PRINCIPAL COORDINATING INVESTIGATOR

The Principal Coordinating Investigator (PCI) of the study takes responsibility for the study. She or he will serve as speaker and make day to day management decisions. She or he will

inform the Country Coordinators, the ESCMID EITaF and/or ESCMID executive board of all major developments and changes in policy or procedures.

COUNTRY COORDINATORS

Country coordinators will liaison with scientific societies and other epidemiological studies in all countries contributing patients. The coordinate contributing centers and reach out to local government and interest groups. Reach-out will be made to ID and/or virological societies in each country. In general, one or two coordinators per country should suffice. If no official coordinator is determined for a country, the PCI may appoint the first investigator to recruit patients as coordinator. All major decisions and scientific publications will be made after consulting with the Country Coordinators.

BOARD OF INVESTIGATORS

Sites enrolling at least 5 patients and at least 5% of the overall study population will be invited to send a delegate to the BoI. If sites later fall below the threshold of 5%, members of the BoI will retain membership status for one further year. Two positions in the Board of Investigators will be reserved for ESCMID and/or EITaF board members.

All major decisions and scientific publications will be made after consulting with the Board of Investigators (BoI). Should the PCI step down from her or his position, become unable to fill the position or receive a vote of no confidence by 2/3 of the BoI, the BoI can decide to elect a new PCI that will receive full ownership and control over the study and the data set.

8. AUTHORSHIP POLICY

This study was not designed with a focus on scientific merits, but to rapidly build a relevant clinical dataset that can help improving and focusing patient care during the onslaught of the pandemic. Most results and analyses will be directly published via the project homepage and in clinical working groups. However, more important observations and general conclusions should also be published in peer-reviewed journals to further extend readership.

As described in **Section 7**, parts of the data set will be published on a regular basis after rigorous deidentification for all collaborators. The **Public Database** will only comprise very selected data items and will be open for everyone, while the **Scientific Database** will be stored in a secure webspace on the project homepage after double deidentification and aggregation. To gain access to Scientific Database, researchers will have to accredit themselves as researchers with a track record in public health, epidemiology, infectious diseases or related clinical care and guarantee to uphold all rules of this protocol and all applicable laws and regulations. They are also not allowed to further share the data directly. Analysis should be performed online via Jupyter Book, a download of the Scientific Database to a secure location under control of the requesting investigator is an alternative.

Analysts and scientists will be encouraged to coordinate activities with the BoI to avoid redundant action and align with the publication strategy of the BoI. Everyone performing analyses will be encouraged to share and publish statistical scripts for community peer review.

Peer-reviewed journal publications of the data set should follow the overall principle of having named authorships for the investigators behind the analysis and the project statistician and as many members of the BoI as possible based on ICJME recommendations. The named group will add “on behalf of the LEOSS study group”, with a full list of BoI members, Country Coordinators, and further contributors in the acknowledgements.

9. CONTACT INFORMATION

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<p>Collaborating entities</p>	<ul style="list-style-type: none"> • Deutsche Gesellschaft für Infektiologie (DGI) • ESCMID Emerging Infections Task Force (EITaF)

10. REFERENCES

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