Subject Information Sheet and Informed Consent Form A

Title of the study: Assessing Spread of COVID-19 and Post-vaccination Monitoring in a Representative-sample of the Population and a Fragile Population

Acronym: *ORCHESTRA Luxembourg*

Sponsor: Luxembourg Institute of Health (LIH)

Principal Investigator: Prof. Dr Rejko Krüger, MD

Contact Prof. Dr Rejko Krüger for more detailed information:

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Tel: +352 26 970 800 (during working hours: 8h-17h)
Email: orchestra.luxembourg@lih.lu

1 INTRODUCTION AND PURPOSE OF THE STUDY

COVID-19 is an infectious disease caused by the coronavirus (SARS-CoV-2). This virus and disease were unknown before their appearance in Wuhan, China, in December 2019. Due to the rapid virus spread all over the world, the World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on January 30th 2020. In May 2021, the illness has affected over 160 million people globally and claimed more than 3 million lives worldwide.

The CON-VINCE study was designed to assess the prevalence and dynamics of the spread of Covid-19 within the Luxembourgish population, and we thank you for participating in this important work that has allowed us to provide a comprehensive insight into the evolution and transmission of the disease over an extended timeframe. This present study will act as a direct follow-on from CON-VINCE as we explore the long-term effects of both COVID-19 and post-vaccination monitoring on the Luxembourgish population.

The present study is part of the ORCHESTRA project (https://orchestra-cohort.eu/), a three-year international research project co-ordinated by the University of Verona and aimed at tackling the coronavirus pandemic. The ORCHESTRA project aims to deliver sound scientific evidence for the prevention and treatment of infections caused by SARS-CoV-2 by using questionnaires to assess epidemiological, clinical, environmental, socioeconomical, and psychosocial features. These items need to be collected to understand both the people and how their social, economical and psychological environments has been affected throughout the pandemic. Additionally there will be biosampling for microbiological, immunological and genotypic aspects

of the population. This will be achieved within ORCHESTRA Luxembourg through questionnaires and biosampling.

This study will be conducted at a local level by the Luxembourg Institute of Health (LIH) and the University of Luxembourg (UL)/Luxembourg Centre for Systems Biomedicine (LCSB). The main goal of the ORCHESTRA Luxembourg study is to examine the immune response linked to vaccination over time, the impact on serological status, via biosampling and the long-term impact of COVID-19 on epidemiological, socio-economic and psychological aspects of the pandemic, via questionnaires, within Luxembourg, and then to compare this information with multiple cohorts across the European Union.

The study is separated into two arms, arm **A** is the representative sample of the general population which is a direct follow-up to the CON-VINCE study and the arm **B** is the fragile population, which is focused on people with Parkinson's disease. **This subject information sheet and informed consent form is related to arm A: the representative sample of the general population, and a direct follow-up to the CON-VINCE study.**

The purpose of this document is to inform you about the study details, including what you will need to do if you decide to participate. Based on this information, you will be able to decide whether or not you wish to participate. Your participation is entirely voluntary. If you choose to participate in this study, you may withdraw at any time without giving your reason. This study has been authorized by the Ministry of Health and by the National Research Ethics Committee (CNER) on 11/06/2021.

This study is subject to the Grand-Ducal regulation of 30 May 2005 and to the law of 8 March 2018 (art. 27).

2 HOW WILL THE STUDY BE CONDUCTED?

The 'representative sample of the population' arm of ORCHESTRA Luxembourg, referred to as the "study" in the rest of the document, is based on your voluntary participation.

If you are enrolled in the study, you will be asked to fill out a questionnaire (approx. 32 min) and provide dried blood spot sampling and an optional stool sample via home collection. **This procedure will be repeated at 3, 9 and 21 months.**

The first contact will be via email to invite you to participate in the study. In order for you to agree to participate, you are receiving this information sheet. For the next steps, we use a secured online interface to ask you to provide some personal information (name, surname, date of birth, mobile phone number, email, and postal address) in case your personal information has changed since your participation in the CON-VINCE study. Your consent will be requested for your participation to this study via a secured online interface. If you have any questions about the study and your involvement, you can contact the study team by phone or email, as indicated on the top of this document.

Once you agreed to take part in this study and provided the above information, you will receive another email to complete an online questionnaire. The questions will concern the following domains (duration approx. 32 minutes to complete):

- SARS-CoV-2 Vaccine
- Epidemiological factors and travel history
- Demographics and socioeconomic questions
- Comorbidities and current medication
- Symptoms onset and initial clinical signs of SARS-CoV-2
- Knowledge, perception of risks related to SARS-CoV-2
- Current clinical symptoms
- Psychological questionnaires

Additionally, after you complete filling out the questionnaire, you will receive a dried blood spot home collection for homesampling and the following samples will be collected:

- Blood

You will have the possibility, if you wish, to donate the following samples for the research as well:

- A stool sample (You will receive a special collection kit at home, with the help of which you can collect a small amount of stool and send it to the biobank by mail.)

Samples will be stored in the LIH's biobank, the Integrated Biobank of Luxembourg (IBBL) for research purposes. The implementation of app-based questionnaires for the follow-up assessments over the study period are envisioned, giving you the possibility to answer to the follow-up questionnaires via the Orchestra app instance in the "PatientConcept" mobile application. The PatientConcept app is provided by NeuroSys GmbH, Germany. Using this mobile application is optional, and the same data will be collected as in the browser. It was developed to give the participants an additional platform option to fill out the questionnaires.

3 USE OF MY SAMPLES

As part of this research project, specific tests are foreseen on your samples; e.g.: virology (to check if the virus is present, and which virus variant is present) and, serology (analysis of your blood antibodies that indicate if your immune system encountered and reacted against the coronavirus and/or the vaccine).

New knowledge about the SARS-CoV-2 infection is gained daily through the efforts of researchers at the international level. For this reason, it is currently impossible to list precisely which tests will be performed on the samples you donate, however, all future analysis and testing on these samples will be limited to projects focusing on infectious diseases and immunology.

If you give consent for other research as well, your samples may be used for other medical research programs conducted by the LIH or other duly authorized national or international research organizations or biobanks, for academic and/or commercial purposes, whether in the field of COVID-19 research or in the field of infectious diseases and immunology, depending on the options you choose in the consent form.

The principles described in this document will therefore also apply to future medical research projects as long as they are scientifically relevant, except that for future third party research projects:

- information on such future medical research may not be available, and the Data Controller, Principal Investigator, sponsor and approving authority may be different;
- in case of withdrawal of consent, you will not be able to request the destruction of your samples already transferred to biomedical research projects.

Your samples and data will only be used for research projects that have received the formal approval from the National Research Ethics Committee (CNER) and the Ministry of Health, and that do not contradict the choices you have expressed in the informed consent form. In any case, the recipients of the data will not have access to information that allows your identity to be associated with these samples and data.

4 WHAT ARE THE GENETIC ANALYSES?

Genes are present in every cell of the body. They give the body the instructions it needs to function and repair itself, and they are passed from parents to children and from cell to cell as new cells are created in the body. Sometimes the genes in the body can change, and if this change can be passed from parents to children, it is called a germline mutation.

Researchers want to understand how diseases can be linked to the genes we all carry. In this case, the question is to know whether the genetic make-up of individuals can influence the susceptibility towards the

coronavirus or the course of COVID-19 disease. Understanding these links may lead to the development of more effective and personalized tests and treatments for each patient. For this type of research to be carried out, it is necessary to analyse and compare the genes of healthy and sick people. In this context, the use of Next Generation Sequencing (NGS) techniques allows a precise and exhaustive analysis of the genome that will contribute to the discovery of genetic modifications, even subtle ones.

If you also agree, genetic analyses may be carried out in the framework of secondary use of your samples. In this context, a fortuitous discovery of a germline mutation (mutations or aberrations that could not only affect my future health, but also that of my children, siblings, parents) could also be discovered. Therefore, you are asked to authorize the genetic analysis of your samples.

In this context, it's possible that we encounter incidental findings. An Incidental Finding (IF) can be defined as a "finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study." Genetic and clinical IFs can be of potential importance for the health of the participant. IFs are not specifically targeted and there is no obligation of the researcher to search for such findings actively. It is also of importance to stress out, that methods used in the research study are prima facie intended concerning the research questions of the study.

In such cases, we follow the guidelines published by the National Research Ethics Committee (CNER) of Luxembourg, where, if the researcher discovers an IF, he/she will inform the principal investigator (PI) of the study, who will act according to your preference "to be informed" or "not to be informed". If you indicate in the consent form that you prefer "to be informed" the PI (who in this case is the study physician) will communicate the finding to you within 15 working days. If you indicate that you prefer "not to be informed", no action is required in case of an IF. Your decision is fully respected. Finally, at any time during the study, you can change your mind and communicate the decision to the study team.

5 WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS?

There are no significant risks associated with this study. The table below lists all of the risks associated with the collection procedures associated with taking your samples, but these risks are **RARE**.

Procedure – Collection of samples	Associated risks
Blood sampling	Pain, bruising, tiredness or fainting, and infection
Stool sampling	No known risks
Entering data on an online application	Minimal risks* associated by entering data on an online application

* there are risks associated with the fact that the study involves the recording of data online (hacking, risk of endangering the confidentiality of health and other personal data). This risk is low, but there is no such thing as zero risks. The LIH and the University of Luxembourg have implemented extensive data protection measures to minimize this risk. These measures are explained in the section "Confidentiality and Protection of Personal Data".

6 WHAT ARE THE BENEFITS OF PARTICIPATING IN THE STUDY?

You may not benefit directly from participating in this study.

However, our study will inform you about your antibody status directed against the SARS-CoV-2 virus. Please be aware that the presence of antibodies against the new coronavirus in your blood does not necessarily

mean that you are immune. Since the SARS-CoV-2 is a new virus, further research is needed to better understand whether, and if so, for how long antibodies protect against the virus.

Your participation in this study is voluntary. You will not receive any compensation for your participation in this study, nor further developments resulting from this study. Your participation is important because you are the source of the information we need to improve our understanding of infectious diseases such as the current COVID-19.

7 CONFIDENTIALITY AND PROTECTION OF PERSONAL DATA

As part of this study, your personal data will be collected and analysed to achieve the scientific objectives of the study.

The LIH and LCSB/UL are jointly responsible for the collection, analysis, and processing of your personal data, and ensure their protection in accordance with the General Data Protection Regulation (EU) 2016/679 of 27 April 2016, applicable as of 25 May 2018 known as the "GDPR" and any subsequent text replacing or supplementing this text (in particular the law of 1 August 2018 on the organisation of the National Commission for Data Protection and the implementation of the GDPR).

What data do we collect?

Your participation in the study involves only the collection of personal data that is necessary for answering the objectives of this scientific study, as described in section 2 above. This will also include the data previously collected as part of the CON-VINCE study.

In particular:

- At the time of your registration, the following data will be collected to verify that you meet the criteria to participate in the study and create your account in the application: date of birth, contact details (name, first name, mobile phone number, email, postal address). The personal identification information will be collected for the purpose of recontacting you to inform you about your test results and future appointments within this study. We have the legal obligation to inform the competent authorities of any coronavirus-positive tests for taking the necessary procedures. The personal identification information will also be used to recontact participants regarding future studies but only if the participant has agreed to be contacted regarding future studies.

On what legal basis do we process your data?

The use of your personal data is necessary to achieve the objectives of the study, which we are conducting in the public interest and for the purposes of scientific research (art. 6.1e and art. 9.2j of the GDPR.).

Who has access to your data?

Apart from the Study's principal investigator and the authorised members of his team working under his responsibility, only the following categories of persons will be able to access your data in relation to their respective duties:

Names or data that directly identifies you (first name, last name, address, telephone number, etc.):

- The study's clinical research team, and the principal investigator of the study will have access to the study's correspondence table, linking your identity data to the code assigned to you for the study.

Coded (pseudonymised) data:

- The principal investigator of the study at the LIH/IBBL and the LCSB/UL and the team working under his/her responsibility,

- The other Study partners (ORCHESTRA consortium: e.g: Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich; the full list of members belonging to the ORCHESTRA consortium is available on https://orchestra-cohort.eu/),
- Other external researchers or research bodies, in the private or public sector, as required to meet the needs of the Study or for future scientific research purposes (under no circumstances will we give them data that would reveal your identity).

We also provide access to your pseudonymised data to service providers who perform services on our behalf. These organisations are bound by stringent security and confidentiality obligations, as required by the law, and the services they provide are subject to contractual agreements.

For instance, we will offer you the possibility to fill in the questionnaire on the Orchestra instance of the "PatientConcept" mobile application.

Orchestra mobile application:

- The Orchestra mobile application is an instance of the "PatientConcept" application, provided by the company Neurosys GmbH, with a registered office located at Hulm, Germany (https://neurosys.de/). You will be able to download this mobile app free of charge in the Apple or Google app stores.
- The provider (NeuroSys GmbH) will only have access to pseudonymised data to transfer them to the secure and encrypted servers of the LCSB/UL, where the data will be stored. No personal identifiable information (name, surname, date of birth, phone number, email, and postal address) will be collected through the app. The data captured by the app will only be pseudonymised answers to the questionnaires. NeuroSys cannot re-contact you directly.
- When you download the "PatientConcept" application, your mobile phone automatically assigns you a unique security code, providing additional security during data exchange. This code is stored locally on the participant's personal device. Only when you give this code exclusively to the Orchestra study team, it will be possible to link your Orchestra participant ID to your responses.
- The LCSB/UL and the LIH will implement appropriate safeguards to protect your pseudonymised data, including the unique security code. Such safeguards include a prior assessment of the provider (considered a processor) regarding the GDPR and a data processing agreement requiring warranties from the provider. Identification of participants by the provider or other third parties is extremely difficult.
- Your personal data will be kept until the end of the study (2023) in the provider's servers in Germany and will be deleted afterwards. The provider needs to temporarily store your pseudonymised data.

Your data will not be used for any fully automated decision-making processes or for any profiling purposes.

Finally, in cases where particular inspections or audits need to be carried out, the competent authorities may also have access to your personal data.

What are your rights?

You have the right to access and rectify your personal data. In certain cases (according to the conditions laid down by law), you have additional rights to object to the way your data is used, to request the deletion of your data, to request the restriction of certain aspects of the processing of your data, to retrieve your data with a view to passing it on to a third party (right of portability). If you wish to exercise your rights, you may contact the principal investigator or his designated representative.

Finally, you have the right to lodge a complaint with the National Commission for Data Protection (CNPD) concerning the processing of your personal data.

For any request for information concerning the processing of your personal data by the LIH or LCSB/UL, you can contact the Data Protection Officer by e-mail at dpo@lih.lu or dpo@uni.lu, or by post at the following address:

LUXEMBOURG INSTITUTE OF HEALTH

Protection des données

1A-B, rue Thomas Edison

L-1445 Strassen

Luxembourg

Or

UNIVERSITÉ DU LUXEMBOURG

Protection des données

Maison du Savoir

2, Avenue de l'Université

L-4365 Esch-sur-Alzette

How do we protect your personal data?

LIH and LCSB/UL implement appropriate security measures, depending on the sensitivity of the data concerned, to protect your data against the risk of unauthorised access, loss, fraudulent use, disclosure, alteration, or destruction of your data.

Your data will be treated in a strictly confidential manner. They will be pseudonymised, i.e., a confidential reference code will be used instead of your name. This code alone does not allow you to be directly identified and will only be used for the scientific processing of your data. At no time will your identity appear in a document intended for the public or other institutions. The correspondence table establishing the link between the reference code and your name will be kept by the Principal Investigator in a confidential manner.

The LIH and LCSB/UL also apply the principle of data segregation, i.e., identification data on the one hand and research data, on the other hand, are stored on different secure servers in order to minimize the potential risks of re-identification. Despite all security efforts, the risk of a data breach is not zero but can be described as very low.

How long do we keep your data?

Your personal data that are not directly identifiable (pseudonymised data) will be kept for a period of 15 years from the end of the sample and data collection scheduled for May 2038. Thereafter, the need for further retention of this data for further processing for research purposes (in the area of infectious diseases and immunological research as you choose in the informed consent form) will be reassessed upon submission to the National Research Ethics Committee (CNER) by 2038.

Concerning your directly identifying personal data (e.g., first name, surname or contact details):

- If you do not wish to be recontacted for possible participation in future research/clinical studies, the link between your identification number in the study and this personal data will be removed 5 years after the end of the sample and data collection.

- If you agree to be recontacted for possible participation in future research/clinical studies, the need to keep this personal data will be evaluated every 5 years.

In the event that you no longer wish to participate in the study, your samples collected prior to the withdrawal of your consent may be retained and used in the study unless you object. In this case, they will be destroyed. However, if any of your samples has already been used in the study, they can no longer be removed from the study.

Data transfers outside the European Union

Your data may be transferred outside the European Union when this is necessary for the implementation of the research or the exploitation of its results. Only anonymous data or data that does not allow you to be directly identified (coded or pseudonymised data) will be transmitted outside the European Union.

It is possible that certain countries outside the European Union/European Economic Area do not offer the same level of privacy protection as your country. In such cases, LIH and LCSB/UL will put in place appropriate measures to ensure the protection of your personal data (for example, by including standard data protection clauses in its contracts, by complying with codes of conduct or by complying with a certification scheme) or will rely on your explicit consent.

For more detailed information on the appropriate measures implemented by the LIH, you can send a written request to the LIH Data Protection Officer by e-mail to dpo@lih.lu.

For more detailed information on the appropriate measures implemented by the LCSB/UL, you can send a written request to the Data Protection Officer of the University of Luxembourg by e-mail to dpo@uni.lu.

8 COSTS ASSOCIATED WITH YOUR PARTICIPATION

If you decide to participate in this study, there will be no additional cost to you or your insurance company. Visits and procedures identified as being specific to the study are the responsibility of the sponsor.

9 INSURANCE

As the sponsor, the Luxembourg Institute of Health (LIH) has taken out civil liability insurance for this study (Zurich Insurance plc, Belgium Branch, Da Vincilaan 5, B-1930 Zaventem).

10 YOUR DECISION TO PARTICIPATE

Your decision whether or not to participate in this study will not affect the quality of care you receive. If you decide to take part in this study, you may end your participation at any time, and you will not be required to give reasons for your decision.

In order to participate in the study, we are seeking your consent online. Please read the consent form and tick the boxes that correspond to your wishes. You can download this document at any time.

If you decide to participate in this clinical study, we ask that you:

- Cooperate fully in the conduct of this study.
- Not withhold any information about your health condition, the medications you are taking, or any symptoms you may have.

If you would like more information about the study, you can contact the research team at the number indicated at the beginning of this form.

Informed Consent Form

Validated by Prof. Dr. Rejko Krüger :

_____

Signature

- I declare that I have read and understood the information described above.

- I understand that I have the possibility to download a copy of this document, as well as the general information for participants.

- I declare that I have received a clear description of the purpose and nature of the study and am aware of what is expected of me as a participant in this study.

- I attest to have had sufficient time to think about it and to discuss it with a person of my choice.

- I understand that I can call the number mentioned in the Information leaflet to ask all the questions about the study that came to my mind

- I fully understand that I am free to leave the study at any time without having to justify my decision and without suffering any material or moral prejudice. I will simply inform the Principal Investigator or the investigative team via the contact options indicated in the top of this questionnaire.

- I understand what type of data will be collected during this study and I understand that any personal information collected in the context of this study will be treated in a strictly confidential manner, in accordance with the General Data Protection Regulation (EU) 2016/679 of 27 April 2016, applicable as of 25 May 2018 (known as the GDPR) and any subsequent text replacing or supplementing this text (in particular the law of 1 August 2018 on the organisation of the National Commission for Data Protection and implementation of the GDPR).

- I accept that the results of this study may be the subject of scientific communications or publications. I am aware that presentation of the study results can in no way allow my direct or indirect identification.

- I voluntarily consent to participate in this study on the basis of the terms and conditions described in the attached information leaflet.*

  ❑ YES ❑NO

  **If you select "no", you are not eligible to participate in the study.*

- I agree that my samples may be collected and given to LIH/IBBL.*

  ❑ YES ❑NO

  **If you select "no", you are not eligible to participate in the study.*

- I authorise the LIH/IBBL and LCSB/UL to use my samples for further research in the broader field of infectious disease and immunological research.

  ❑YES ❑NO

- I agree that my data and samples may be transmitted in an anonymized form outside the European Union where the legislation in force concerning the protection of personal data may be less strict than that of the European Union.

  ❑ YES ❑NO

- I agree to be recontacted for possible participation in future studies.

  ❑ YES ❑NO

- I am aware that no genetic analysis on my sample is foreseen in the frame of this study, but I agree to the genetic analysis by a Next Generation Sequencing techniques (NGS) on my samples in an amendment to the primary study, targeting on COVID-19 subjected to the approval of the Ministry of Health and National Research Ethics Committee (CNER) in Luxembourg.

  ❑ YES ❑NO

- I am aware that no genetic analysis on my sample is foreseen in the frame of this study, but I agree to the genetic analysis by a Next Generation Sequencing techniques (NGS) on my samples in future research

projects related to infectious diseases and immunology subjected to the approval of the Ministry of Health and National Research Ethics Committee (CNER) in Luxembourg.

❑ YES ❑NO

- In case of fortuitous discovery of a germline mutation (mutations or aberrations that could not only affect my future health, but also that of my children, siblings, parents etc.), I consent to this information being communicated to me by my treating physician, to discuss the possible implications and to be referred to a local geneticist if necessary.

  ❑ YES ❑NO

In making my decision, I confirm that I have been fully informed and understand that the researcher is under no obligation to actively search for genetic mutations in my sample(s) and that the discovery of such a mutation does not constitute a diagnosis. It is also at this time that I will be contacted again if I checked "yes" above. Finally, I confirm that I have been informed that I may reconsider my decision at any time.

→ Consequences of my decision:

If I answer "no", I will not receive any information about these chance discoveries, nor will my relatives be informed.

If I answer "yes", I will be informed of the incidental finding(s) by my treating physician / the study physician / a geneticist. I will then be invited to discuss the possible implications and be referred to a local geneticist if necessary.

- If the answer to the previous question is 'yes', and in the event that a germline mutation is identified and I am unable to receive this information personally (including if I am deceased at the time this information is identified), I wish to designate a family member (representative) to whom these results could be communicated, who could discuss the implications with my treating physician, and be referred to a local geneticist

  ❑ YES ❑NO

Name of my representative: _____

If I answer "yes", it means that I agree that my representative can receive such information, discuss the implications with my treating physician, and be referred to a local geneticist.