Telemedically assisted sampling of COVID-19 patients - Is the sampling quality sufficient? An interventional randomized method comparison study

---

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO)[1].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk category A according to HRO Art.7
Project Leader:	PD Dr. med. Walter Zingg, Leitender Arzt Klinik für Infektionskrankheiten und Spitalhygiene, Universitätsspital Zürich, Rämistrasse 100, 8091 Zürich Walter.Zingg@usz.ch, +41 76 419 40 18
Co-Investigators:	Dr. med. Christian Eisenring (local investigator) Dr. med. Michel Bielecki Dr. med. Thibault Lovey Dr. med. Fabian Kraxner Charles Winiarski, PhD

Version Nr	Version date	Modified without version change	Description, comments	Control
3.0	14.04.2022		Revised version	CE

PROTOCOL SIGNATURE FORM

Study Title	*Telemedically assisted sampling of COVID-19 patients - Is the sampling quality sufficient? An interventional randomized method comparison study*

The project leader and Principle Invistigator have approved the protocol version *1 (dated 25.12.2021)* and version 2 (dated 10.01.2022) and version 3 (dated 14.04.2022) and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1] [2], current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

Sponsor and Project leader:

PD Dr. med. Walter Zingg

Date: 14.04.2022 Signature:

Principle and local Investigator

Name: Dr. med. Christian Eisenring

Date: 14.04.2022 Signature:

Table of Contents

GLOSSARY OF ABBREVIATIONS

AES	*Advanced Encryption Standard*
BASEC	*Business Administration System for Ethical Committees*
CRF	*case report form*
Ct	*cycle threshold*
EBPI	*Institut für Epidemiologie, Biostatistik und Prävention*
FOPH	*Federal Office of Public Health*
GSS	*guided self-sampling*
H0	*null hypothesis*
H1	*alternative hypothesis*
HCP	*healthcare professional*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
NP	*nasopharyngeal*
OP+N	*oropharyngeal and nasal*
PCR	*polymerase chain reaction*
RT	*realtime*
SD	*standard deviation*
SOP	*standard operating procedure*
TLS	Transport Layer Security
USS	*unsupervised self sampling*
VOC	*variant of concern*
μs	*mean in the standard treatment group*
μe	*mean in the experimental treatment group*
d	*non-inferiority limit*

1 BACKGROUND AND PROJECT RATIONALE

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) pandemic has resulted in more than 3.8 billion registered tests, 275 million positive cases, and 5 million deaths worldwide.[4,5] It will most likely remain for months or years.[6,7] Early and regular testing has been an important pillar of secondary prevention, since the beginning.[8] The current global emergence of the Omicron variant of concern (VOC), is rewriting the pandemic history because of the increased viral load and transmission. [9] Current projections indicate that COVID-19 hospitalizations are likely to be higher in the next six months than in the last six months.[10] Low vaccination rates foster new mutations and thus, reduce the effectiveness of vaccination. This puts older generations again at higher risk[11] and shifts the timeline of the pandemic by at least several months. [12,13]

As a consequence of the spreading of Omicron VOC, the 2G+ rule has been in effect in Switzerland, since December 20, 2021, meaning that in all publicly accessible cultural, sports, recreational, and entertainment areas, even double vaccinated and individuals who recovered more than four months ago are obliged to present a negative test, to be exempted from the mask requirement indoors.[14] The new measures taken by Switzerland in response to the increasing number of omicron cases place an additional burden on the testing infrastructure, patience, and satisfaction of dually vaccinated, asymptomatic individuals as they adjust their daily lives as best they can to the circumstances with regular testing.

Regular testing is therefore expected to become a part of our lives to allow public operations.[8] The testing infrastructure is currently costly to operate and maintain. In addition, the lack of availability of adequately trained personnel and insufficient accuracy and quality of testing urged some test centers to halt operations.[15] This situation has exacerbated in decentralized, rural areas where the density of test centers results in longer travel distances and inherent transmission risks on public transport.[16] However, this pandemic has also fostered solutions in the form of e telemedicine with enormously increased applicability, especially rural areas.[17] Several emerging issues, such as the use of technology by older adults, the availability of high-capacity Internet access, and support for telemedicine, can be overcome in the near future to increase the benefits of telemedicine.[18,19]

In Israel, the uptake of regular testing increased with the introduction of rapid home and self-testing. Especially in areas of high viral activity, self- and home-tested children allowed the schools to continue operating.[20,21] Also, other Western countries, including the United Kingdom, the United States of America[22] and Switzerland, introduced video-assisted sampling as a self-testing strategy.[23,24] In Switzerland, this has been well received by broad segments of the

population; however, only polymerase chain reaction (PCR) tests had been medically approved to generate a certificate.[25] The advantages are obvious: less exposure of symptomatic to healthy individuals in test centers, increased low-risk accessibility for e.g. immunocompromised people, consistent implementation of isolation and quarantine obligations without interruption for early termination based on negative testing[26]. The available private information technology and communication infrastructure with smart devices reduce the provision of costly state infrastructure.

Studies comparing self-sampling were published, but none compared autonomous self-testing with guidance by healthcare specialists to sampling by healthcare professionals in a randomized controlled trial.[27–30] Non-inferiority of oral + nasal vs. nasopharyngeal sampling has been proven[31]. However, the question of whether telemedically supervised testing with SARS-CoV-2 Rapid Antigen Tests is non-inferior to the same tests being carried out by trained personnel in test centers is still open for debate.

With this study, we aim to compare and evaluate the reliability and sampling quality of self-performed rapid tests for professional use compared to professional sampling by healthcare personnel. This will be done by comparing cycle threshold (Ct) values of both housekeeping genes and SARS-CoV-2.[32]

A solution that builds on the capacity of existing laboratories may be implemented with a high level of safety and minimizes the risk of transmission in rural areas.
This fuels hope that medical personnel will be relieved of the burden of jointly managing the pandemic as a national and global challenge.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

Our hypothesis is that, applying a strict standard operating procedure (SOP, attached), guided oropharyngeal + nasal (OP+N) self-sampling (GSS) is non-inferior to nasopharyngeal (NP) or OP+N sampling performed by health care professionals (HCP), and that guided OP+N sampling is superior to unsupervised OP+N self-sampling (USS).

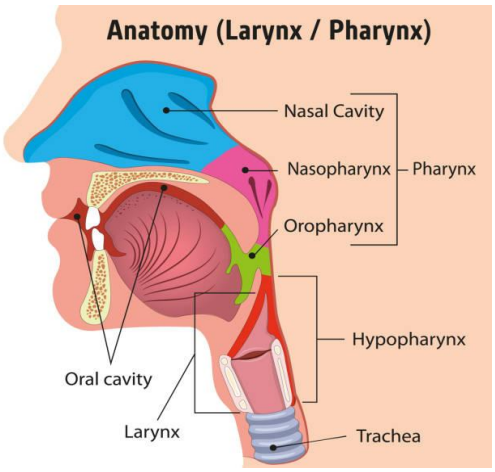


Figure 1: Anatomy of Larynx/Pharynx[33]

- OP+N GSS is non-inferior to nasopharyngeal (NP) sampling performed by HCP
- OP+N GSS is non-inferior to OP+N performed by HCP
- OP+N GSS is superior to unsupervised OP+N USS

We are also interested to know if the difference between the sampling techniques is the same depending on the SARS-CoV-2 viral load (low, medium, high).
Another secondary endpoint will be in how many people a correctly executed nasopharyngeal sampling is possible. Due to lack of comfort, deviation of septum, as well as nasal polyps in a small percent of the population, we hypothesize that in a majority of people it is not possible to correctly execute a nasopharyngeal sampling.

2.2 Primary and secondary endpoints

The Ct-value is defined as the number of cycles required for a signal to cross the detection threshold and can be used as a surrogate for sampling quality, as it allows to quantify the amount of material that is being extracted.

Primary endpoints:

- Concordance of positive/negative samples in antigen tests with GSS, USS, and HCP-based samples.

Secondary endpoints:

- Housekeeping gene Ct comparison based on sampling method between samples based on GSS, USS, or HCP
- ORF1ab/RdRp-, E-, N-, and S genes Ct value comparison based on sampling method between samples based on GSS, USS, or HCP
- Qualitative analysis of perceived sampling accuracy established with a short form
- Detected variant of concern
- Case report form (CRF) assessing basic demographics and variables of interests as indicated separately in the CRF form
- Prevalence of variants of concern
- Immunization status
- Travel destinations in the passed three months
- n of people in which a nasopharyngeal sampling is possible correctly (ratio)

2.3 Project design

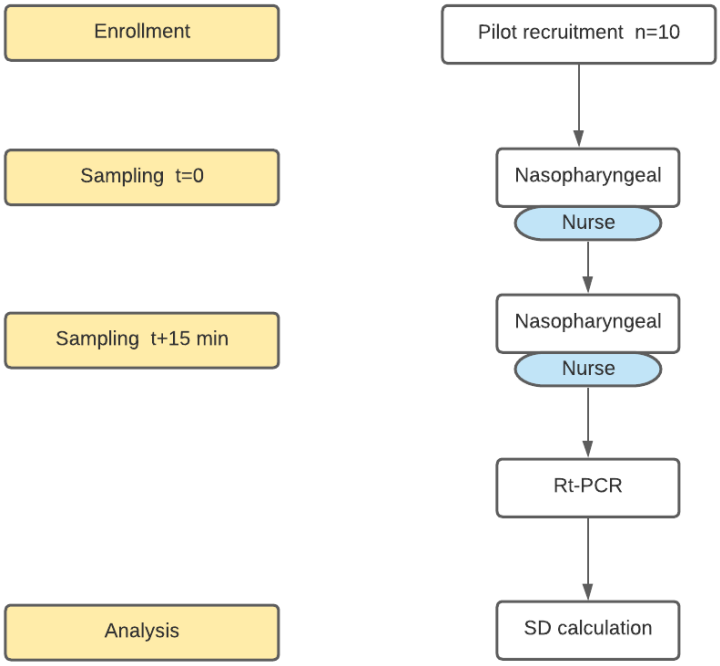
This is a single-center, randomized, controlled study at a Swiss test station.

2.3.1 Piloting

In order to assess the sampling quality by HCP or telemedically guided self-sampling, Ct values obtained in RT-PCR analysis of a COVID-19 assay, a housekeeping gene can be used for reference.

Hence, for the first part of the study, we will recruit 10 people in which we will perform an OP+N sampling at two-time points, 15 minutes apart, and compare the Ct values of these two values to calculate the standard deviation and see if the produced SD*1.96/√(Sample size)

equals the margin of error. Our 95% confidence interval (CI) will be standard deviation (SD)+/- the margin of error.



Alternatively, we will pool confirmed RT-PCRs of two/three swab samples into one and spike them with SARS-CoV-2 standard. Next, we do as many repeats of the same sample on RT-PCR comparing housekeeper and SARS-CoV-2 genes. The advantage here is that we will have controlled starting biological material and the resultant SD / 95% CI will concern only the analytical and laboratory process variability. With the first approach, we will test SD of the swab procurer too, along with the interference coming from the analytical process (lab, instruments, sample storage).

2.3.2. Randomized telemedical and HCP sampling

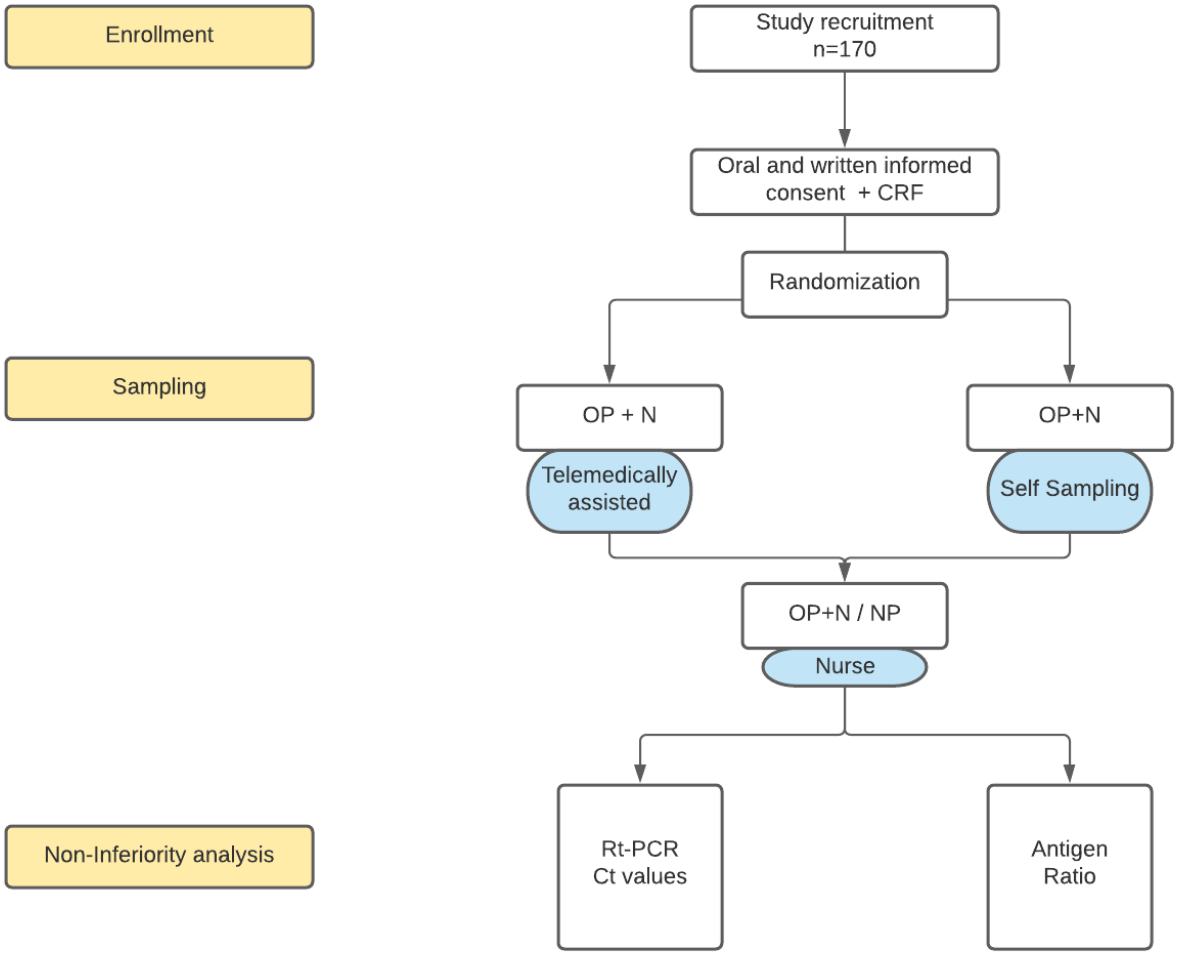
After giving informed consent by signing the consent form, patients will be randomized to either OP+N GSS - or to OP+N USS.
After performing either procedure, they will continue to be sampled by HCP OP+N and HCP NP.
We will start the assessment with the self-sampling methods in order to reduce bias that could occur if they experience the HCP's sampling.

Written instructions on how to perform a self-test will be provided, representing the instructions that come along with a commercially available rapid test set. An instructional online video tutorial or similar would also account as the latest state of the art.[30] However, this has not yet been implemented comprehensively with all available test sets that are currently being distributed across Switzerland.

Furthermore, to avoid bias in the sampling procedure, exclusively one HCP at the testing station will be designated as the study's sampling expert. The HCP will perform the NP and OP+N sampling sequentially in a previously randomized order.

The telemedical guidance will be exclusively done by the same HCP in order to minimize interoperability differences. The standardized telemedical sampling will be conducted at the same test station, in a separate empty room in which a computer will be placed with instructions on how to connect for the telemedical consultation.

Figure 1: Study chart



During each sampling procedure, the patients will either undergo OP+N GSS or OP+N USS for PCR analysis, as well as for antigenic testing. This means each participant will be sampled a total of six times within 15 minutes from different locations in the upper respiratory tract. Concordance of results between sampling by GSS vs. USS vs. HCPs will be assessed.

As the difference in time between the samplings can influence the Ct value, the sampling process will only be started when the HCP and the telemedical supervisor are ready. The three different samples will be stored in the test station refrigerator between 2°C-8°C before transport.
A grouping of samples will ensure that temperature changes are consistent between samples from the same participant.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

All patients, regardless of symptoms, who present themselves at the Test-station SARS-CoV-2 testing will be offered to participate in the study.

Study inclusion criteria;

- Written informed consent
- Patients visiting the test-station for a SARS-CoV-2 test
- Consent to comply with the study protocol
- Age of 18 or older

List the study exclusion criteria:

- Refusal to comply with the study protocol
- Digital illiteracy (i.e. patients who would never use telemedicine as they do not feel competent enough to use the necessary tools)
- Not German or English speaking
- People trained in the use of rapid diagnostic tests (HCP, biologists) will be excluded to reduce bias[30]

3.2 Recruitment, screening and informed consent procedure

The participating test station in Olten receives approximately 100 patients per day for PCR and/or antigen testing. The population is mixed as both asymptomatic people, as well as symptomatic people, frequent the facility for SARS-CoV-2 testing. The recruitment will happen by the local investigator in daily clinical practice. All costs for tests performed within the framework of the study will be financed by the study. A payable travel certificate will be issued for unchanged costs. Participation in the study and spending time on it is voluntary, free of charge and at no cost to the study participants. However, each study participant will receive a voucher for free PCR testing at a later date.

Patients who wish to have a COVID test can register online at least one day in advance for predefined time slots for appointments (via the Onedoc-Software, Geneva, Switzerland).

Immediately after registration, the potential test participants will be informed about the study either by telephone or by e-mail based on their contact details, with delivery of the written study material if they are interested, giving them more than 24 hours to contemplate whether they want to participate.

At the consultation, a personal oral and written briefing about the study goals and study design, as well as the informed consent form will be given to the participants. They are invited to date and sign if they are willing to participate and have no further questions, and express to have understood the content and do agree with it. A copy of the signed document will be given to the study participant. The consent form will be stored as part of the study records.

Participants will not receive financial compensation for the participation in this study. However, each study participant will receive a voucher for free PCR testing at a later date.

We shall end recruiting either when reaching the necessary sample size or no later than October 30th, 2022.

3.3 Study procedures

- The recruitment phase will start immediately after the approval of this study by the cantonal ethical committee.
- Sampling will be performed by a licensed and trained HCP.
- The telemedical supervision will be guided by a licensed medical doctor.
- The three different samplings will occur randomly in sequence (NP and OP+N by HCP and either OP+N USS or OP+N GSS by the participant)
- To ensure comparable results and reduce biases, all procedures will happen in the same testing premises. The HCP will always sample the participants. The same doctor will always guide the participants through self-sampling.
- Registration starts at least 24 hours before the telemedical consultation. The consultation will take about 10 minutes, sampling will take place at two time points, 15 minutes apart, and filling of the final questionnaire will take another 15 minutes. The rapid test result is announced immediately and the COVID-19 certificates will be issued according to cantonal guidelines. The PCR test evaluation takes a maximum of 24 hours and test results will be automatically communicated to the participant after analysis. Positive results and symptomatic people will be reported to the federal office of public health (FOPH) through the online reporting tool. The whole process from registration to the communication of the final PCR result will take approximately 48 hours for each patient.
- In case of a positive rapid test result, the FOPH is informed by the HCP on site through the online reporting system. In case of a positive PCR test, the FOPH and cantonal authorities are automatically informed by the analyzing laboratory.
- We aim to finalize the study by December 31st, 2022.
- Multiple laboratories have been contacted for participation in the study and the best fit is currently being evaluated.

Possible biases include mainly sampling bias and selection bias which are accounted for in the study design via randomization and through tight exclusion criteria. A list of possible confounders can be found in table 1 (Appendix).

3.4 Withdrawal and discontinuation

Participants are free to withdraw their consent at any time without giving any reason. In case of withdrawal of consent, their sample will be destroyed and their data will be deleted from the database.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

4.1.1 Randomization

To ensure allocation concealment, randomization will be performed with a block of 170 in a 1:1 allocation ratio by a web-based independent randomization software (Random Allocation version 1.0). Patients will be randomly assigned to either OP+N GSS or to OP+N USS. Instruction on the assigned procedure will be kept in sealed opaque envelopes labeled with sequential study numbers and opened right before swab-testing.

4.1.2 Sample size

The SD of the mean of Ct values for RT-PCR analysis of multiple samples is not clearly defined in the literature and varies between studies.[34,35]

If there is truly no difference between the standard and experimental treatment, then 85 patients per group are required to be 90% sure that the lower limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will be above the non-inferiority limit of -3.

We, therefore, estimated a standard error of six that accounts for this variance. In addition, the limit of non-inferiority was set at three according to clinical significance.

Results will be stratified by symptom status, age, and sex.

4.1.3 Hypothesis

Primary outcome

NP HCP vs OP+N HCP

H0: μe – μs ≤ -d -> μ(NP HCP ct) - μ(OP+N HCP ct) ≤ -3
H1: μe – μs > -d -> μ(NP HCP ct) - μ(OP+N HCP ct) > -3

OP+N HCP vs OP+N GSS

H0: μe – μs ≤ -d -> μ(OP+N HCP ct) - μ(OP+N GSS ct) ≤ -3
H1: μe – μs > -d -> μ(OP+N HCP ct) - μ(OP+N GSS ct) > -3

OP+N HCP vs OP+N USS

H0: μe – μs ≤ -d -> μ(OP+N HCP ct) - μ(OP+N USS ct) ≤ -3
H1: μe – μs > -d -> μ(OP+N HCP ct) - μ(OP+N USS ct) > -3

Secondary outcome:

We will stratify the primary outcome by viral load (low, medium, high).

4.1.4. Statistical test

A variant of a paired student t test or Wilcoxon test (if non-normal distribution) with exchange of null and alternative (relaxed) hypotheses will be used as a non-inferiority test to assess differences in cycle threshold (Ct, considered as a log2-transformed measure of the amount of viral RNA load) between the NP and OP/N samples (HCP and GSS). Stratification for possible confounders will be done using logistic regression.

In order to show agreement between the approaches and estimate the limits of agreement and those are not too large, different graphical methods, such as Bland Altman diagrams will be used to show agreement between the approaches.

4.2. Handling of missing data

Analysis is based on intention-to-treat assumption. Collected data until drop-out will be included for further analysis.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki[3], the principles of Good Clinical Practice, the Human Research Act (HRA)[2] and the Human Research Ordinance (HRO)[1] as well as other locally relevant regulations. The Project Leader and the Sponsor both acknowledge their responsibilities.

5.2 Notification of safety and protective measures (HRA Art. 15, HRO Art. 20)

If, during the research project, circumstances arise which could jeopardize the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the benefits, all the measures required to ensure protection are to be taken without delay.
The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.5 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days. All biological materials and health-related data are anonymized upon the termination of data analysis.

5.7 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge, except for claims that arise from misconduct or gross negligence. (Art. 12 HRO).

---

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

Already before the COVID-19 pandemic, the Swiss healthcare system has been undergoing a digital transformation. Digitalization enables decentralized living, e.g., in a home office, making life in remote areas more attractive. The desire for proximity to green nature, sufficient living space and a garden of one's own has continuously gained in importance. On the one hand, the population assesses Switzerland's healthcare system as particularly well equipped for digitalization; on the other hand, deficits in implementation are also perceived, especially in rural areas.[36]

Rural areas of Canada, Finland, Ireland, Sweden, Scotland, Northern Ireland, Faroe Islands, Iceland, Greenland and Norway are also very positive about decentralized living. It allows progress, optimizes organization, and responds effectively to healthcare challenges with favorable economic outcomes.[37] Similarities with Switzerland are that access to healthcare and schooling are capable of turning rural areas more attractive for young families to build resilience and encourage them to stay. This process is facilitated through digitalization.[38] From a global perspective, digitalization of healthcare is on the rise, in keeping with increased testing capacities for COVID-19, which has proven essential to successful management of the pandemic.[39]

In rural Australian areas, pending test results restrict everyday life. Emergency and family visits are denied in case of a pending COVID-19 test result and quarantine occurs when there is a suspected case of COVID transmission, while waiting for test results.[40] Cumbersome testing is a global challenge especially in rural regions.[41] Challenges comprise diagnostic insufficiency and low testing capacity since COVID-19 testing as well as treatment centers, are mainly situated in the urban areas.[42,43] Lack of easily applicable testing capacity leads vulnerable groups to delay testing and seek medical care only at advanced stages of the disease, resulting in poorer outcomes.[44] There is clearly a local and global desire for large-scale testing through fast, accurate and affordable diagnostic. A proven strategy to increase testing capacities is to foster public-private partnerships.[42]

The use of self-testing with reactive antigen SARS-CoV-2 home tests is instrumental in enabling governments around the world to relieve some restrictions to a reasonable degree and open their economies and societies despite the advancing pandemic. Effective testing can also be critical during a rapid surge in cases, as evidenced in India and USA, with governmentally authorized reactive antigen SARS-CoV-home tests.[45] Self-administered nasal swab rapid tests are on the rise and bring relevant profits worldwide in the healthcare sector such as less personnel effort, infrastructure, protective equipment and exposure of healthcare workers, healthy individuals and symptomatically ill individuals. This brings about not only positive impact on the health of each individual but also on a larger scale with advantageous social and economic outcomes.[45]

The collected genetic study data will be handled as described above and the participants are not exposed to additional risks compared to standardized testing as described below. This, in keeping with the freely provided test-result and certificate suggests a fair balance for the study

participant, also from a public health and economic point of view. Incidental findings would in case of appearance be discussed with the study team and if need be with the Ethics Committee. Study participation is voluntary and may be revoked without explanation as described above.

6.2 Risk-Benefit Assessment

Self-sampling is already a common practice in Switzerland, in many European countries and in many countries around the world. There are no additional risks to standardized OP+N swab-testing to the study participants. The risk of each swab is already minimal and will be kept minimal through professional instruction and supervision by specifically trained HCP. However, the testing takes place six times on the same day, that means that possible inconveniences such as local pain or discomfort is six times more likely.

No financial compensation is provided, but the cost of testing will be compensated. The individual study participant will not have a direct profit of this clinical study to compare different testing modalities. However, in the long term the participants and future patients may contribute to acquisition of results concerning a simplified and less invasive testing method that may be well integrated into everyday life. Future patients may benefit from a better understanding of COVID-19 disease diagnostics.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

To reduce biases strict SOPs will be implemented.

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

The procedures will be done by specially trained physicians and scientists as health care experts from the Teststation.

7.2 Data recording and source data

The source data will consist of the study CRF, a baseline questionnaire. Clinical data will be entered into REDCap, an online CRF. Access is only possible with a username and password. De-indentified data will be downloaded after study completion and stored for ten years on University Hospital Zurich (USZ) secure server. This server is behind the institutional firewall.

The project data will then be transferred and stored permanently on REDCap in the REDCap secure database.

Patient data will be stored in the REDCap database, behind the University of Alberta firewall, and institutional data protection standards of University of Alberta, Canada will apply. This is a password protected, secure database that can track changes. The server has an SSL security certificate that allows encrypting the data that is transferred between the client and the server. Regular back-ups of data can be created from REDCap database.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to the above-mentioned investigators who require the data to fulfill their duties within the scope of the research project. On the CRFs and other project-specific documents, participants are only identified by a unique participant number. The document containing the keys linking the ID and the patient will be encrypted and accessible only by the principal investigator.

Biological material in this project is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel.

All identifiable data will be uploaded to REDCap and once the project is archived at the REDCap Server in Alberta-Canada, only the data manager at the Clinical Trials Center of the Universitätsspital Zürich, Ashlesha Sonpar, will have access.

7.4 Retention and destruction of study data and biological material

Samples will not be kept after analysis, they will be discarded by the laboratory according to the internal processes for biohazardous materials. Biological material will be destroyed at the latest on 31.12.2022.

The study data will be stored for 10 years after termination of the research project. Access will be limited to the principal investigator.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

This project is privately funded by the local investigator, Dr. med. Christian Eisenring.

There is a conflict of interest between one of the investigators (Dr. med. Michel Bielecki, CEO of GobiX GmbH) who has a remote diagnostics startup and provides the testing facilities.

9 REFERENCES

1. Council SF. Ordinance on human research with the exception of clinical trials (Human Research Ordinance, HRO).

2. Human Research Act (HRA).pdf.

3. WMA declaration of Helsinki – ethical principles for medical research involving human subjects [Internet]. [cited 2021 Dec 23];Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

4. Total COVID-19 tests [Internet]. Our World in Data. [cited 2021 Dec 21];Available from: https://ourworldindata.org/grapher/full-list-total-tests-for-covid-19

5. COVID live - Coronavirus statistics - worldometer [Internet]. [cited 2021 Dec 21];Available from: https://www.worldometers.info/coronavirus/

6. Chowdhury R, Heng K, Shawon MSR, et al. Dynamic interventions to control COVID-19 pandemic: a multivariate prediction modelling study comparing 16 worldwide countries. Eur J Epidemiol 2020;35(5):389–99.

7. Ravi N, Cortade DL, Ng E, Wang SX. Diagnostics for SARS-CoV-2 detection: A comprehensive review of the FDA-EUA COVID-19 testing landscape. Biosens Bioelectron 2020;165:112454.

8. Schnyder N, Baggio S, Rossegger A, Endrass J, Gonçalves LC, Inauen J. Adherence to public health measures during the COVID-19 pandemic: the pivotal role of behavioural science. smw.ch [Internet] Available from: https://sci-hub.ren/https://smw.ch/op-eds/post/adherence-to-public-health-measures-during-the-covid-19-pandemic

9. Tian D, Sun Y, Zhou J, Ye Q. The Global Epidemic of the SARS-CoV-2 Delta Variant, Key Spike Mutations and Immune Escape. Front Immunol 2021;12:5001.

10. Charumilind S, Craven M, Lamb J, Sabow A, Singhal S, Wilson M. When will the COVID-19 pandemic end? [Internet]. 2020 [cited 2021 Dec 20];Available from:

https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/when-will-the-covid-19-pandemic-end

11. Assessment RR. Assessment of the further emergence and potential impact of the SARS-CoV-2 Omicron variant of concern in the context of ongoing transmission of the Delta variant of concern in the EU/EEA, 18th update. 2021;Available from: https://sci-hub.ren/https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-assessment-further-emergence-omicron-18th-risk-assessment-december-2021.pdf

12. Omicron_The global response_nature_2021.pdf.

13. Omicron is bad but the global response is worse. Nature 2021;600(7888):190.

14. Bundesrat D. Coronavirus: Bundesrat beschliesst weitergehende Massnahmen [Internet]. [cited 2021 Dec 21];Available from: https://www.admin.ch/gov/de/start/dokumentation/medienmitteilungen.msg-id-86544.html

15. Medinside [Internet]. [cited 2021 Dec 20];Available from: https://www.medinside.ch/de/post/kanton-bern-will-die-schnellen-nasen-tests-verbieten

16. Ceci A, Muñoz-Ballester C, Tegge AN, et al. Development and implementation of a scalable and versatile test for COVID-19 diagnostics in rural communities. Nat Commun 2021;12(1):4400.

17. Bestsennyy O, Gilbert G, Harris A, Rost J. Telehealth: A quarter-trillion-dollar post-COVID-19 reality? [Internet]. 2020 [cited 2021 Dec 19];Available from: https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/telehealth-a-quarter-trillion-dollar-post-covid-19-reality

18. Malwade S, Marri M, Gundamraj R, et al. Telemedicine in Your Pocket: An Alternative Teleconsultation Tool in a Pandemic and in Resource-Poor Settings. Telemed J E Health [Internet] 2021;Available from: http://dx.doi.org/10.1089/tmj.2021.0443

19. Seifert A, Batsis JA, Smith AC. Telemedicine in Long-Term Care Facilities During and Beyond COVID-19: Challenges Caused by the Digital Divide. Front Public Health 2020;8:601595.

20. All students to get multiple home COVID tests for regular screening — TV [Internet]. 2021 [cited 2021 Dec 20];Available from: https://www.timesofisrael.com/all-students-to-get-multiple-home-covid-tests-for-regular-screening-tv/

21. Israel hands every child a DIY virus test, in bold bid for safe school restart [Internet]. 2021 [cited 2021 Dec 20];Available from: https://www.timesofisrael.com/israel-hands-every-child-a-diy-virus-test-in-bold-bid-for-safe-school-restart/

22. CDC. Self-testing [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2021 Dec 21];Available from: https://www.cdc.gov/coronavirus/2019-ncov/testing/self-testing.html

23. Coronavirus (COVID-19) testing before you travel to England [Internet]. [cited 2021 Dec

20];Available from:
https://www.gov.uk/guidance/coronavirus-covid-19-testing-for-people-travelling-to-england

24. Navica App & BinaxNOW™ COVID-19 Ag test card [Internet]. [cited 2021 Dec 20];Available from:
https://www.globalpointofcare.abbott/en/product-details/navica-binaxnow-covid-19-us.html

25. Art. 24e67 Probenentnahme für molekularbiologische Analysen auf Sars-CoV-2 [Internet]. [cited 2021 Dec 21];Available from: https://www.fedlex.admin.ch/eli/cc/2020/438/de#art_24_e

26. Bundesamt für Gesundheit BAG. Coronavirus: Isolation und Quarantäne [Internet]. [cited 2021 Dec 21];Available from:
https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/isolation-und-quarantaene.html

27. Lindner AK, Nikolai O, Kausch F, et al. Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with self-collected nasal swab versus professional-collected nasopharyngeal swab. Eur Respir J [Internet] 2021;57(4). Available from:
http://dx.doi.org/10.1183/13993003.03961-2020

28. Nikolai O, Rohardt C, Tobian F, et al. Anterior nasal versus nasal mid-turbinate sampling for a SARS-CoV-2 antigen-detecting rapid test: does localisation or professional collection matter? Infect Dis 2021;53(12):947–52.

29. Savage HR, Finch L, Body R, et al. A prospective diagnostic evaluation of accuracy of self-taken and healthcare worker-taken swabs for rapid COVID-19 testing [Internet]. bioRxiv. 2021;Available from: http://medrxiv.org/lookup/doi/10.1101/2021.12.06.21267356

30. Tonen-Wolyec S, Dupont R, Awaida N, Batina-Agasa S, Hayette M-P, Bélec L. Evaluation of the Practicability of Biosynex Antigen Self-Test COVID-19 AG+ for the Detection of SARS-CoV-2 Nucleocapsid Protein from Self-Collected Nasal Mid-Turbinate Secretions in the General Public in France. Diagnostics 2021;11(12):2217.

31. Desmet T, Paepe PD, Boelens J, et al. Combined oropharyngeal/nasal swab is equivalent to nasopharyngeal sampling for SARS-CoV-2 diagnostic PCR. BMC Microbiol 2021;21(1):31.

32. Nossmann M. Optimization of a molecular diagnostic strategy to verify SARS-CoV-2 infections by RT-qPCR. Journal of Laboratory Medicine 2020;44(6):349–56.

33. LCOSMO. Human larynx and internal pharynx anatomy head illustration, close [Internet]. iStock. [cited 2021 Dec 23];Available from:
https://www.istockphoto.com/de/vektor/menschliche-larynx-und-innere-pharynx-anatomie-kopf-illustration-schlie%C3%9Fen-ideal-gm1204429898-346557196

34. Mahallawi WH, Alsamiri AD, Dabbour AF, Alsaeedi H, Al-Zalabani AH. Association of Viral Load in SARS-CoV-2 Patients With Age and Gender. Front Med 2021;8:608215.

35. Wagenhäuser I, Knies K, Rauschenberger V, et al. Clinical performance evaluation of SARS-CoV-2 rapid antigen testing in point of care usage in comparison to RT-qPCR.

EBioMedicine 2021;69:103455.

36. Hermann et al, Stadt-Land-Monitor_SOTOMO_2021.pdf.

37. How remote communities turned the challenges of peripherality to their advantage during COVID-19 [Internet]. RSA Main. 2021 [cited 2021 Dec 23];Available from: https://www.regionalstudies.org/news/blog-how-remote-communities-turned-the-challenges-of-peripherality-to-their-advantage-during-covid-19/

38. Karlsdottir_CONSIDERATIONS ON REGIONALLY VARIED IMPACTS OF COVID-19 IN NPA REGIONS_2021.pdf.

39. Adebisi YA, Rabe A, Ekpenyong A, Okereke M, Sarah OA, Others. Towards 90-90-90 Target: COVID-19 and HIV Response in Africa. J Infect Dis Epidemiol 2021;7:191.

40. COVID-19 coronavirus: Remote Aboriginal communities travel [Internet]. [cited 2021 Dec 23];Available from: https://www.wa.gov.au/organisation/department-of-the-premier-and-cabinet/covid-19-coronavirus-remote-aboriginal-communities-travel

41. Australian Government Department of Health. Impact of COVID-19 in remote and regional settings [Internet]. 2020 [cited 2021 Dec 23];Available from: https://www.health.gov.au/resources/publications/impact-of-covid-19-in-remote-and-regional-settings

42. Adebisi YA, Oke GI, Ademola PS, Chinemelum IG, Ogunkola IO, Lucero-Prisno DE Iii. SARS-CoV-2 diagnostic testing in Africa: needs and challenges. Pan Afr Med J 2020;35(Suppl 2):4.

43. Ogunkola IO, Adebisi YA, Imo UF, Odey GO, Esu E, Lucero-Prisno DE 3rd. Rural communities in Africa should not be forgotten in responses to COVID-19. Int J Health Plann Manage 2020;35(6):1302–5.

44. Adebisi YA, Ekpenyong A, Ntacyabukura B, et al. COVID-19 Highlights the Need for Inclusive Responses to Public Health Emergencies in Africa. Am J Trop Med Hyg [Internet] 2020;Available from: http://dx.doi.org/10.4269/ajtmh.20-1485

45. Goggolidou P, Hodges-Mameletzis I, Purewal S, Karakoula A, Warr T. Self-Testing as an Invaluable Tool in Fighting the COVID-19 Pandemic. J Prim Care Community Health 2021;12:21501327211047782.

46. Kochhar R. The American middle class is stable in size, but losing ground financially to upper-income families. Pew Research Center 2018;6.

47. COVID-19 Antigen Rapid Test [Internet]. [cited 2021 Dec 25];Available from: https://lucerna-chem.ch/COVID-19-Antigen-Rapid-Test

Appendix

Schedule of assessments

Time	*>-1 day*	*0*	*+1*
Visit	*Information*	*Testing*	*Results*
oral and written Information	+		
Written consent		+	
check inclusion-/ exclusion criteria		+	
Participant Characteristics		+	
Procedures		+	
Questionnaire		+	
Sampling		+	
Result communication		+	+ *(PCR)*

Shell Table 1: Potential confounders

Confounding Variables	Type of variable
Age	Continuous
Sex	Binomial
Mobility impairment	Nominal
Occupation	Categorical
Socioeconomic status	Continuous
Highest level of education attained	Ordinal

Financing

Type	Source	Amount in CHF	Percent
public	Privately funded by local investigator	30‘000	100