Study protocol

Health after COVID-19 in the European region North-Tyrol & South-Tyrol

Health after COVID-19 in the
European region North-Tyrol & South-Tyrol

Short title ReCOVerT

version: 3.0

date: 29.04.2021

Commitment to confidentiality

The information provided in this clinical trial protocol is strictly confidential and is made available exclusively to potential reviewers, investigators, participating investigators and their study team, as well as the medical director of the conducting hospital, health authorities and ethics committees for inspection, review or implementation. Publication or disclosure to third parties without the prior written consent of the sponsor is expressly prohibited. Upon signature of the clinical trial protocol, the regulations of this clinical trial protocol are binding for all parties.

Table of contents

List of abbreviations 3
1. Abstract 4
2. Background 6
2.1. The SARS-CoV-2 pandemic 6
2.2. Clinical spectrum of acute COVID-19 7
2.3. Recovery and long-term sequelae after COVID-19 9
2.4. Data on "SARS-CoV-2-recovered" individuals in Tyrol and South-Tyrol 10
3. Aim of the study and hypotheses 12
4. Methods 14
4.1. Study design 14
4.2. Contribution of individual project partners 14
4.3. Inclusion/Exclusion criteria and recruitment for participation 14
4.4. Questionnaire and data management 15
4.5. Ethics approval 16
4.6. Biometrics and statistics 16
5. Level of Originality 17
6. Cooperations 18
7. Work plan and time schedule 18
8. Scientific quality and contributions 19
9. Safety aspects and ethics approval 20
10. Gender related aspects 20
Annex 1 References 21
Annex 2 Existing research facilities and employees, costs 24
Study Center A: 25
Study Center B: 26
Annex 3 Clinical Trial Synopsis 27

List of abbreviations

ACE2	Angiotensin Converting Enzyme 2
Ao. Univ. Prof.	Associate university professor
APP	Application
ARDS	Acute respiratory Distress Syndrome
Cand. Med	Candidata/Candidatus medicinae (Latin), meaning “medical student)
cm	Centimetres
Co-PI	Co-Principal investigator
CoV-2	Corona Virus 2
COVID	Corona Virus Disease
COVID-19	Corona Virus Disease 2019
CXR	Chest X-ray
Doz.	Lecturer
Dr.	Doctor
e.g.	exempli gratia (Latin, meaning “for example”)
EK Nr.	Ethics committee number
FWF	Austrian Science Fund
GP	General Practice
H2O	Water
i.e.	id est (Latin, meaning “that is”)
IL6	Interleukin 6
JAMA	Journal of the American Medical Association
kg	Kilogram
LFHS	„Landesfachhochschule für Gesundheitsberufe“ – State College for Health Professions
Long-COVID	Corona Virus Disease
ml	Millilitres
NO	Nitric oxide
PCR	Polymerase chain reaction
PEEP	Positive end-expiratory pressure
PhD	Doctor of Philosophy
Prim.	“Primarius” meaning Chief Doctor
Prof.	Professor
RKI	Robert Koch Institute
RR	Respiratory Rate
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome – Corona Virus 2
TV	Tidal Volume
UK	United Kingdom
WHO	World Health Organization

1. Abstract

Theoretical framework: COVID-19, the infectious disease caused by the novel coronavirus SARS-CoV-2, is probably the biggest global economic, social, political and medical challenge at present. With worldwide over 64 million confirmed cases, Tyrol and South Tyrol were among the first major COVID-19 hotspots in central Europe facing great burdens to the health system. Since the start of the pandemic knowledge about the spectrum of symptoms and the course of the infection is growing, but there are still limited data available on the phenotype of the acute infection, patient´s trajectories and long-term sequelae.

Objectives of the study: The main aims of this joint project of the Medical University of Innsbruck, Tyrol, Austria, and the Institute of General Practice, Bolzano, Italy, are the description and comparison of disease manifestation, convalescence and long-term consequences of SARS-CoV-2 positively tested probands by means of an anonymised survey with voluntary participation in the two European COVID-19 hotspots.

Patients and methods: In a descriptive observational study, volunteer participants of Tyrol (Austria) or South Tyrol (Italy) with confirmed SARS-CoV-2 infection are included in an anonymized cross-sectional web-based survey. The country-specific approaches were approved by the institutional review board at Innsbruck Medical University (EK Nr: 1257/2020) and the Ethics Committee of Bolzano (EK Nr:118/2020) and the study was registered by the initiating centre at ClinicalTrials.gov (NCT04661462), indicating the centre in Bolzano as cooperation partner.

Contribution of individual project partners:
The multidisciplinary team of researchers of the Medical University of Innsbruck is responsible for the establishment of the multi-item questionnaire and set up of a digital platform for an anonymous public online survey. After start-up financing this survey has started in the Tyrolean population (Austria) since the 30th of September and will be openly accessible for up to twelve months.
The South Tyrolean project partner is responsible for country dependent adaption of the survey and is going to recruit probands using the infection registries of general practitioners. By this cooperation, the increased number of cases, the different approaches to recruit participants, individual and comparative statistical evaluations will provide a reliable picture of the health status after COVID-19 in the European region Tyrol & South Tyrol.

Level of innovation: We expect new insights into the course of the novel coronavirus disease, regarding the presentation of the acute disease, recovery and long-term sequelae. In an international comparison, this is the first study characterised by a broad multidisciplinary survey with comprehensive coverage of

various aspects of infection and recovery. The results of this observational study will especially expand knowledge on “Long-COVID” and serve as a basis for improved health care planning.

2. Background

2.1. The SARS-CoV-2 pandemic

COVID-19, the new infectious disease caused by the novel coronavirus SARS-CoV-2, is probably the biggest global economic, social, political and medical challenge at present (Lai et al. 2020). In December 2019, the virus spread rapidly from its potential point of origin in Wuhan, China, across the entire globe and has since left its traces in most nations, including Austria.

In January 2020, the World Health Organisation (WHO) described the problem as an "emergency of the public health system with international scope" and classified COVID-19 as a pandemic on 11 March 2020. On the 8th of December 2020 the COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University (COVID-19 Map - Johns Hopkins Coronavirus Resource Center (jhu.edu)) is counting more than 67 million global cases and more than 1.5 million global deaths.

Total mortality from the disease varies widely, ranging from 0.5% to 7%, depending on the medical infrastructure available, the stringency of the testing according to region and patient age, with mortality appearing to increase with age and comorbidities such as hypertension and obesity (L. quan Li et al. 2020)(Richardson et al. 2020)(Wadhera et al. 2020).

Pathophysiologically, after droplet infection and cellular penetration of the SARS-Cov2 virus via the angiotensin converting enzyme 2 (ACE2) receptor in the nasopharynx, the virus spreads in the nasopharynx, mainly in the respiratory tract. The immune response as a result determines whether an asymptomatic infection, mild infection or severe infection with hyperinflammation, dysfunctional lymphocytes, disrupted epithelial-endothelial barrier, endothelitis and hypercoagulability occurs (H. Li et al. 2020) (Figure 1).

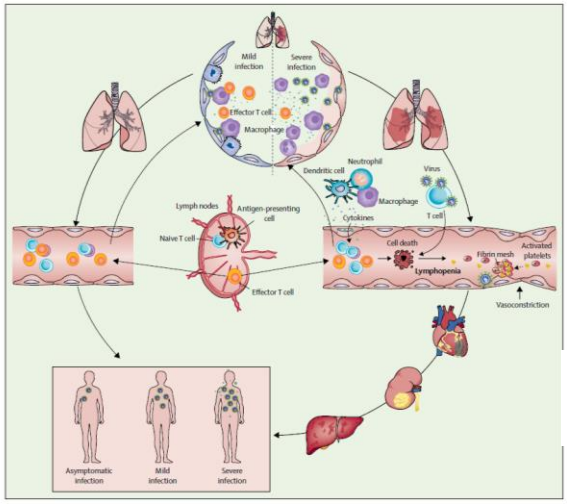


Figure 1: Pathophysiology and phenotype of SARS-CoV-2 infection (5).

2.2. Clinical spectrum of acute COVID-19

While at the beginning of the pandemic in Europe the focus was on the recognition of the clinical triad "cough, fever, shortness of breath" with assignment to a respiratory phenotype (Table 1, (Rello et al. 2020), meanwhile a broad spectrum of clinical manifestations became apparent (Figure 2). However, reports on the distribution of disease symptoms are mainly from hospitalised patients. For example, Chen et al (N. Chen et al. 2020) found fever in 83%, cough in 82%, shortness of breath in 31%, muscle pain in 11%, confusion in 9%, headache in 8%, sore throat in 5%, rhinorrhoea in 4% and diarrhoea in 2%. Common complications include ARDS (17%), septic shock (4%) and a high overall mortality rate of 11%.

As clinically experienced during the initial pandemic phase in Europe, a biphasic course of the disease was described. Initially, there are often only mild symptoms. Between days 7-10, a break-in with renewed fever and rapid respiratory deterioration may occur (J. Chen et al. 2020).

A large proportion of those infected in home quarantine only complains of mild symptoms such as fever and/or cough and it is believed that there is a significant number of untested asymptomatic infected people who may play a major role in the spread of the virus. Surprisingly, patients also present with symptoms of gastrointestinal infection and recently an Innsbruck research group was leading in detecting the virus in stool (Ng and Tilg 2020). Cardiac manifestations are rare, but are associated with high lethality (Shi et al. 2020). Also specific is the increased occurrence of olfactory and gustatory disorders independent of nasal rhinitis as an early and sometimes only manifestation of COVID-19, opening the spectrum of possible neuroinvasive manifestations of SARS-Cov2 (Lechien et al. 2020)(Moein et al. 2020). The latter includes central dysregulation of blood pressure, heart rate and respiratory drive. Invasive forms of necrotising encephalitis have also been described. In addition to infecting the central nervous system, the peripheral nervous system can also be affected in the sense of polyneuropathy (Mao et al. 2020).

Moreover, patients also present with only skin manifestations such as urticaria and fever or show thromboembolic consequences on fingers or toes or viral exanthema (Galvan Casas et al. 2020). Conjunctivitis of the eyes adds to the list of symptoms, which continuously increases (Hu, Patel, and Patel 2020).

Phenotype	Proportion	Clinical Fetaures
1	80-85% of symptomatic patients	Fever, headache, mild respiratory symptoms, sore throat, no hypoxemia, normal chest X-ray (CXR), excellent prognosis.
2	~80% of hospitalised patients	Mild hypoxemia, minor, usually bilateral infiltrates on CXR, up to 15% may progress quickly to type 3
3	~15% of hospitalised patients	Moderate to severe hypoxemia and tachypnoea, high IL6 and other inflammatory markers. May progress to types 4 or 5
4	~2/3 of patients needing mechanical ventilation	Severe hypoxemia requiring mechanical ventilation, normal lung compliance, good response to NO. Prone position of little benefit. TV > 6ml/Kg allowed. RR < 20 bpm. PEEP < 10cm H2O.
5	~1/3 of patients needing mechanical ventilation	High procalcitonin, may be increased if mechanical ventilation is delayed in severely hypoxic patients, more in keeping with classical ARDS. Protective ventilatory strategy and prone position indicated.

Table 1: Clinical respiratory phenotypes of COVID-19 (adapted from (Rello et al. 2020)**).**

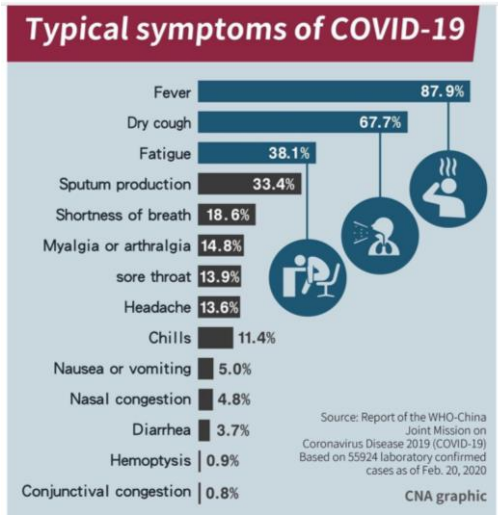


Figure 2: Typical symptoms of acute SARS-CoV-2 infection reported from the WHO-China Joint Mission. (Source: who-china-joint-mission-on-covid-19-final-report.pdf).

Most of the reports so far refer to in-patients; data on the clinical spectrum of non-hospitalised patients who have been quarantined are scarce. In the "COVID-19-Case-Cluster-Study" in Heinsberg, Germany (https://www.aerztezeitung.de/Nachrichten/Die-Erkenntnisse-aus-der-Coronavirus-Studie-in-Heinsberg-408507.html), published only in digital media, an infection rate of 15% was found in 509 participants, but every 5th positively tested subject was asymptomatic. A high rate of asymptomatic patients was also recently recorded by the team around Prof. von Laer in the context of antibody testing in the Ischgl population (Tyrol) (https://science.apa.at/rubrik/medizin_und_biotech/Ischgl Studie_42_4_Prozent_sind_Antikoerper-positiv/SCI_20200625_SCI39451352255218286).

2.3. Recovery and long-term sequelae after COVID-19

The recovery of COVID-19 may depend on the severity of the disease (longer convalescence in viral pneumonia, intensive care, severe neurological involvement, severe cardiac involvement, thromboembolism), however, the total duration of convalescence and the development of long-term damage is unclear.

In patients who had suffered from viral pneumonia requiring hospitalisation, but who were not required to undergo intensive care, the morphological changes on discharge from hospital are declining, but there are persisting symptoms and impairments in lung function (Carfì, Bernabei, and Landi 2020)(Mo et al. 2020). Writing in JAMA, a team of researchers from Italy reported that nearly nine in 10 patients (87%) discharged from a Rome hospital after recovering from COVID-19 were still experiencing at least one symptom 60 days after onset. They found that only 13% of the 143 people were completely free of any symptoms, while 32% had one or two symptoms, and 55% had three or more (Carfì, Bernabei, and Landi 2020). Although none of the patients had fever or any signs or symptoms of acute illness, many still reported fatigue (53%), dyspnoea (43%), joint pain (27%), and chest pain (22%). Two fifths of patients reported a worsened quality of life. It is unclear to what extent an increased development of interstitial lung disease occurs and is being prospectively investigated at our team at the University Hospital Innsbruck (CoviLD-study, NCT 04416100). The long-term course of intubated patients is not yet available. The first rehabilitation programmes have been established, with scarce reports on their outcome so far (J. Li 2020). Irritating are requests from patients who are considered to have recovered and who suffer from coughs, odour disorders, headaches, sensitivity disorders etc. weeks after infection. This expecially includes patients who were in home quarantine. Furthermore, psychiatric, psychological and psychosocial consequences of the illness itself and its circumstances (e.g. quarantine) must be recorded (Ahmed et al. 2020). An increased rate of neuropsychiatric consequences such as even demyelination or post-viral

fatigue syndrome is feared (Troyer, Kohn, and Hong 2020). There is also concern about the consequences of persistent hyperinflammation and/or hypercoagulability, which may be associated with an increased rate of vascular events in the first weeks after surviving the disease (Bajwah et al. 2020).

Those affected themselves have joined together on the Internet (#LongCovid) and are looking for recognition of the symptoms, research and rehabilitation (www.LongCovid.org/about). The terminology used to describe long-term effects is still inconsistent. Terms used by clinicians include post-COVID-syndrome (symptoms over 3 weeks) and chronic COVID (symptoms over 3 months), the media is writing about LongCovid or Long Haulers. In the meantime, the first structured studies on possible long-term effects have been published and the term "Long-COVID" is increasingly used to explain lasting effects of COVID-19, that may even present with different syndromes (Mahase 2020b)(Mahase 2020a).
Data from the prospectively UK COVID-19 Symptom Study app revealed ongoing symptoms in 13.3% of 4182 incident cases four weeks after infection (Sudre et al. 2020). The app was developed by the health science company ZOE, and the data are being analysed in collaboration with researchers at King's College London (Menni et al. 2020). Acute symptoms and the course of recovery was followed for 12 weeks. Long-COVID was characterised by symptoms of fatigue, headache, dyspnoea and anosmia and was more likely with increasing age, BMI and female sex. Experiencing more than five symptoms during the first week of illness was associated with Long-COVID. Thus, non-hospitalized COVID-19 illness may result in prolonged illness and persistent symptoms, even in young adults and persons with no or few chronic underlying medical conditions. In an American telephone survey addressed to COVID-19 patients in home quarantine not returning to usual health within 2–3 weeks of testing was reported by approximately one third of respondents (Tenforde et al. 2020). Even among young adults aged 18–34 years with no chronic medical conditions, nearly one in five reported that they had not returned to their usual state of health 14–21 days after testing. In contrast, over 90% of outpatients with influenza recover within approximately 2 weeks of having a positive test result (Petrie et al. 2015). In particular, dyspnoea has been shown to be a significant predictor of long-term symptoms in an unselected COVID-19 population (Cirulli et al. 2020).

2.4. Data on "SARS-CoV-2-recovered" individuals in Tyrol and South-Tyrol

Through central Europe, Tyrol and South-Tyrol occupies a special position because this region was an initial hot spot region. According to the current dashboard database of the Tyrolean and South Tyrolean regional government, on the 29th of April 2021 in total in this region 132.797 Cov-2 infected individuals have been recorded (Coronavirus COVID-19 Dashboard Tirol (arcgis.com); http://www.provinz.bz.it/sicherheit-zivilschutz/zivilschutz/aktuelle-daten-zum-coronavirus.asp. In Tyrol, 57.291 of 60.198 infected individuals were reported as recovered, respectively, in South Tyrol 70.283 of 72.599 infected individuals. The regulatory definition of "recovered" e.g. by the Austrian health

authorities is based on criteria defined by the Federal Ministry - in accordance with the recommendations of the Robert Koch Institute in Germany (RKI; www.rki.de).

Patients who were treated in hospital (severe cases)

- Discharge at the earliest 10 days after the onset of symptoms
- No symptoms for at least 48 hours (no fever or cough)
- 2 tests for SARS-CoV-2 carried out every 24 hours must be negative, i.e. the virus must no longer be detectable in the nasal or throat swab.

Patients in home quarantine (mild cases)

- Removal of domestic isolation only after medical consultation
- Not earlier than 10 days after the first symptoms appear
- No symptoms for at least 48 hours (no fever or cough)

The basis for these decision criteria is primarily the aim to define discharge criteria from isolation to exclude any further risk of infection and has country-specific adaptations. As clinically experienced during the initial pandemic phase in Europe, a biphasic course of the disease was described. Initially, there are often only mild symptoms. Between days 7-10, a break-in with renewed fever and rapid respiratory deterioration may occur (J. Chen et al. 2020). This has also been described to us by patients who have been in home quarantine. It is therefore important that people who are in home quarantine pay attention to their symptoms and seek medical attention immediately if they get worse.
Through close telephone contact, health authorities have tried to record this deterioration of patients in isolation, but no systematic recording of this data is available for scientific evaluation. Furthermore, actively contacting SARS-Cov2-infected patients for a scientific survey was not possible in Tyrol, because of the data protection law.
In addition, the complexity of residuals that are supposedly perceived by the patient as marginal (partly not specified) and the occurrence of secondary diseases are not taken into account here.
Therefore, further regional acquisition of data on the presentation of the disease and the course of recovery is important to better understand this new infectious disease, to initially make a correct allocation to acute care and to plan the care questions of recovery.

The aims of this joint project between the Medical University of Innsbruck, Tyrol, Austria, and the Institute of General Practice, LFHS Claudiana, Bozen, Italy, are the description and comparison of disease manifestation, convalescence and long-term consequences by means of an anonymised survey, which is addressed to SARS-CoV-2 positively tested probands with voluntary participation. The results of this

survey will broaden the scientific knowledge, e.g. on Long-COVID and serve as a basis for improving hospital and community care for patients after COVID-19.

3. Aim of the study and hypotheses

The aim of this study is to establish the disease profile of the acute phase and the course of the disease from data of a comprehensive digital survey, which is addressed to SARS-CoV-2 affected individuals in Tyrol and South Tyrol. This will provide a description of demographic aspects, of symptoms during the acute phase, the convalescence phase and long-term burden of disease.
The anonymised collection of these data serves as a basis for future care questions and is scientifically coordinated on an interdisciplinary basis.

Objectives

- Recording the spectrum of symptoms of acute and post-acute COVID-19 disease in Tyrol and South Tyrol.
- Recording of long-term consequences after surviving acute infection of COVID-19 disease in Tyrol and South Tyrol.
- Recording of the median time to complete recovery.
- Derivation of care questions for the province of Tyrol and South Tyrol in the acute phase (compilation of a spectrum of symptoms to be queried; compilation of risk profiles) and for recovery (compilation of a spectrum of long-term consequences, development of prediction tools, recording of questions on rehabilitation).

Primary hypothesis

80% of Tyroleans and South Tyroleans suffering from COVID-19 have a mild course of the disease with complete recovery after 4 weeks.
The symptom pattern of acute COVID-19 is associated with protracted recovery.

Secondary hypotheses

1. The occurrence of a protracted or severe course depends on the type and number of previous illnesses.
2. The occurrence of a protracted or severe course depends on age.
3. The occurrence of a protracted or severe course depends on gender.
4. Different clusters of initial presentation are associated with different long-term effects.

5. An active smoker status is associated with more respiratory symptoms in the acute phase.
6. An active smoker status is associated with more persistent respiratory complaints in the recovery phase.
7. Patients who report shortness of breath describe a course of the disease lasting longer than one week (as pulmonary involvement occurs in the 2nd week).
8. The rate of vascular complications such as heart attack, stroke, embolism/thrombosis is increased in the weeks following COVID-19 disease.
9. Patients' exercise performance remains significantly impaired for weeks after acute illness
10. 30% of patients describe neurological symptoms at the initial manifestation.
11. Smell and/or taste disorders can remain persistent for months after the acute symptoms have subsided.
12. The occurrence of a protracted or severe course depends on neurological symptoms that occur in the acute phase.
13. Patients report insomnia and increased daytime tiredness after the disease.
14. The questions on the mental health of COVID-19 patients show an increased incidence of mental adjustment disorders.
15. The questions on the current psychosocial situation of COVID-19 patients show a broad spectrum of increased psychosocial stress.
16. Due to the COVID-19 disease and quarantine, treatment and clarification of other diseases had to be postponed.
17. The majority of COVID-19 patients need rehabilitation.

Null hypotheses to be tested:

1. Less than 80 % of COVID-19 patients in Tyrol and South Tyrol do recover four weeks after the onset of symptoms.
2. There are no long-term consequences of COVID-19 disease.
3. The symptom pattern of acute disease is not associated with protracted recovery.

Alternative hypotheses to be tested:

1. 80% of Tyroleans and South Tyroleans suffering from COVID-19 have a mild infection and have fully recovered four weeks after the onset of symptoms.
2. There are long-term consequences of COVID-19 disease.
3. The symptom pattern of acute disease is associated with protracted recovery.

4. Methods

4.1. Study design

This study is a descriptive observational study applying a cross-sectional web-based survey method with two separate recruiting centres (North-Tyrol, South-Tyrol).

4.2. Contribution of individual project partners

The multidisciplinary team of the Medical University of Innsbruck is responsible for the establishment of the multi-item web-based questionnaire and set up of a digital platform (Computer-based Health Evaluation System - CHES (Holzner et al. 2012) for an anonymous public online survey. After start-up financing this survey has started in the North-Tyrolean population (Austria) since the 30th of September and will be accessible until 8 months after the 2nd wave of the pandemic has subsided.

The South Tyrolean project partner is responsible for country dependent adaption of the survey and is going to recruit probands by a different approach via the infection registers of the general practitioners. By this cooperation, the increased number of cases, the different approaches to recruit participants, individual and comparative statistical evaluations will provide a reliable regional picture of the health status after COVID-19 for these two European hotspots.

4.3. Inclusion/Exclusion criteria and recruitment for participation

Inclusion criteria for participation in North-Tyrol:

- Expired COVID-19 infection, diagnosis by PCR from nasopharyngeal/pharyngeal swab or serum antibody test
- Residence in Tyrol
- Age ≥ 16 years

Exclusion criteria:

- Active infection with SARS-CoV-2
- Residence outside North-Tyrol
- Age < 16 years

Recruitment for participation in North-Tyrol: Individuals after SARS-Cov-2 infection are invited by repetitive media calls to participate in the public online survey. An official letter with an invitation to study participation of positively tested individuals was not allowed in Austria due to the Data Protection Act.

Inclusion criteria for participation in South-Tyrol:

- COVID-19 infection, diagnosis by PCR from nasopharyngeal/pharyngeal swab
- Recovery ≥ 2 weeks (no symptoms for at least 48 hours and two negative PCR tests every 24 hours)
- Residence in South Tyrol
- Age ≥ 18 years

Exclusion criteria:

- Residence outside South Tyrol
- Age < 18 years

Recruitment for participation in South Tyrol:

Individuals who fulfill the inclusion criteria are contacted in written form by the general practitioner who has access to the infection register and are invited to participate in the online survey. Moreover, individuals after SARS-Cov-2 are invited to participate in the public online survey by repetitive media calls.

4.4. Questionnaire and data management

An interdisciplinary questionnaire, coordinated with the health authorities, has been created and is enclosed in the version 2.0 "Questionnaire_Health after COVID-19" (13.08.2020) https://cloud.ches.pro/index.php/s/Ny7twTeQ9twkFea. It has the aim to collect the following data: age, sex, family status, height, weight before infection and current, educational status, occupational group, comorbidities (25 items), long-term medication, vaccination behaviour, smoking behaviour, symptoms during acute infection (46 items), duration of symptoms, questions about general health, mental health, psychosocial health, rehabilitation needs, medical care and treatments, subjective assessment of exercise performance, subjective assessment of health impairment, as well as data from free-text response fields. The data is collected digitally in an anonymised form.

The online survey is initiated by means of participant information with details of the examination and data protection measures, see version: ICF_Participant_info_online_ Ges-Cov-19_Version 1_13082020 https://cloud.ches.pro/index.php/s/8f7Zw5MGJDS4AMK

4.5. Ethics approval

The country-specific approaches were approved by the institutional review board at Innsbruck Medical University (EK Nr: 1257/2020) and the Ethics Committee of Bozen (EK Nr:118/2020).

4.6. Biometrics and statistics

Sample size estimation:

In North-Tyrol the total population of SARS-CoV-2 infected patients is 60.198 (according to data of the Ministry of health of the 29th April 2021 (Coronavirus COVID-19 Dashboard Tirol (arcgis.com)). In South-Tyrol, the total population of SARS-CoV-2 infection is 72.599 (47.034 with positive PCR tests), according to the official data of the South Tyrolean Health Trust (https://www.provinz.bz.it/sicherheit-zivilschutz/zivilschutz/aktuelle-daten-zum-coronavirus.asp). In North-Tyrol we will approximately include 1500 to 3000 patients and in South Tyrol between 500 and 1.000 patients. We consider the sample size to be representative for the descriptive and comparative analyses. According to power calculation, for South Tyrol we need a sample size of at least 572 patients to get a 95% confidence interval with a precision of 3% for the primary end point (i.e., 80% of COVID-19 patients fully recovered four weeks after the onset of symptoms), respectively for Tyrol, under the same conditions, we need a sample size of 671 patients. For the secondary endpoints we have to adjust for multiple analyses, and thus, we agreed to allow for a precision of 5%.

Statistics:

The collected data (demographic data, comorbidities, disease-relevant clinical data, course of the disease) are analysed descriptively in each survey cohort. The primary endpoint is the percentage of patients who recovered, defined as “no symptoms at four weeks” after the onset of COVID-19. To answer the primary hypothesis (see section 3. Aim of the study and hypotheses), absolute and relative frequencies are measured. Correlations between parameters and cross-national comparative analysis will be computed using parametric or non-parametric tests depending on the measurement level and distribution of the variables. Regression analysis will be used to evaluate the associations between demographic data, number and type of symptoms, comorbidities, individual recovery trajectories and long-term consequences in each survey cohort.

Demographic and clinical factors as well as symptoms occurring in the first two weeks of acute SARS-Cov2 infection associated with the risk of long COVID in the North-Tyrol cohort will be identified by univariate logistic modelling. From the pool of the significant risk-modifying variables identified this way, a clinically applicable, multi-parameter prediction tool will be developed using a random-tree modelling algorithm. The final long COVID prediction score will be validated with independently acquired data obtained in the South-Tyrol cohort.

Risk assessment and bias:

At the population level, it is critical to quantify the burden of symptoms and recovery of COVID-19 to better assess its impact on the healthcare system. While this study might provide important insight into the disease presentation, a generalization should be considered carefully. First, a representative sample size has to be reached (see sample size estimation above). Second, as already shown by the study from the UK COVID-19 Symptom Study app, the study may be biased by being confined to participants who have a better access to online systems (e.g. the UK app was primarily used by female individuals aged under 70 years) (Sudre et al. 2020). Thus, comparative analysis to confirm stable results through the two different survey cohorts and analysis rebalancing to North-Tyrol and South-Tyrol population demographics have to be performed. Furthermore, a recall bias might affect some of the responses to the survey depending on the study participants' ability to recall the past event (i.e., symptoms of the acute COVID-19 infection).

5. Level of Originality

By this cross-national approach we expect new insights into the course of the new corona virus disease, regarding the presentation of the acute disease, recovery and long-term symptom burden. In an international comparison, this is the first study characterised by a broad multidisciplinary survey with comprehensive coverage of various aspects of infection and recovery. The results of this observational study will especially expand our knowledge on Long-COVID and serve as a basis for improving hospital and community care for patients after SARS Cov-2 infection.

6. Cooperations

As specified in Annex 2 (Research facilities, employees) the presented study is based on a multidisciplinary work and exchange of different medical disciplines cross-nationally (Infectiologists, internists, pneumologists, neurologists, dermatologists, psychiatrists, pediatricians, psychologists, nursing, general practitioners, statisticians and representatives of rehabilitation medicine and health authorities, see http://inneremed2.tirol-kliniken.at/page.cfm?vpath=forschung/gesundheit-nach-covid-19).

The collaborators are representatives of their medical discipline and responsible for the COVID-19 specific questions in the survey as well as the specific discussion of the results.

7. Work plan and time schedule

Center A Medical University of Innsbruck		**Center B Institute of General Practice, Bozen**	
time schedule	**work plan**	**time schedule**	**work plan**
April 2020 to June 2020	Establishment of a multidisciplinary questionnaire		
June 2020 to August 2020	Ethics approval Establishment of the digital platform	August 2020 to October 2020	Country-specific adaption of the questionnaire, Ethics approval
30th September 2020	Start of public online survey, repeated press release is ongoing	November 2020	Country-specific adaption of the digital platform
until January 2021	ongoing possibility of probands to take part in the public online survey	December 2020 to January 2021	Written invitation of 3500 SARS-CoV-2 positive tested probands for participation in the online survey through the general practitioners
February to March 2021	Depending on response and pandemic situation continuation of recruitment (by repeated press release)	February to March 2021	Interim analysis of survey sample and depending on response rate and pandemic situation continuation of recruitment (e.g. repeated press release and communication with GPs)
April to June 2021	Interim analysis or final analysis depending on response and pandemic situation Comparative Analysis with Data from South-Tyrol Preliminary report to health authorities	April to June 2021	Final analysis and preparation of manuscript and report of recommendations to health authorities Comparative Analysis with Data from North-Tyrol
July to August 2021	Final Analysis	July to August 2021	Comparative Analysis with Data form North-Tyrol

	Comparative Analysis with Data from South-Tyrol Preparation of manuscript and report of recommendations to health authorities		
September to October 2021	manuscript revision, international presentation and discussion, development of hypotheses and research proposals for further analytical studies to verify found associations.	September to October 2021	manuscript revision, international presentation and discussion, development of hypotheses and research proposals for further analytical studies to verify found associations.

8. Scientific quality and contributions

The national and international cooperations (see Section 6., Annex 2 and 4 (collaboration letter) provide evidence for scientific quality of the presented proposal.

Prof. Dr G. Weiss and ao Univ. Prof. Dr. R. Bellmann-Weiler (infectiologists), ao Univ.Prof. Dr. Judith Löffler-Ragg and Doz. Dr. Ivan Tancevski (pneumologists), Doz. Dr. Raimund Helbok (neurologist) and Prof. Dr. Barbara Sperner-Unterweger (psychiatrist) are leading academic and clinical experts in COVID-19 (acute and follow-up).

Ao Univ. Prof. Dr. J. Löffler-Ragg ist Co-PI of the CovILD study with Doz. Dr. Ivan Tancevski, a prospective multicenter study aimed at identifying persisting cardio-pulmonary damage in COVID-19 patients after recovery https://clinicaltrials.gov/ct2/show/NCT04416100 - manuscript on 3-months follow up has been accepted for publication in the *European Respiratory Journal* on Nov 18, the flagship journal of the *European Respiratory Society.*

Several different manuscripts on COVID-19 are in preparation, one as co-author currently under review in Cell (https://www.medrxiv.org/content/10.1101/2020.11.09.20228015v1) (please see Publication list attached).

Feldfunktion geändert

9. Safety aspects and ethics approval

This study is an anonymised survey. The participants cannot be identified. No further investigations are planned. Therefore, there are no specific risks or safety aspects for the participants. The country-specific approaches were approved by the institutional review board at Innsbruck Medical University (EK Nr: 1257/2020) and the Ethics Committee of Bozen (EK Nr:118/2020).

10. Gender related aspects

Previous data on severe courses of COVID-19 show an overdominance of men (Kopel et al. 2020). First results of long-term effects, however, show a higher proportion of affected women (Menni et al. 2020). Therefore, the consideration of gender (diversity) is of great importance in COVID-19 disease and recovery. The questionnaire used in this proposal asks for the gender (male, female, diverse) and also included specific questions on pregnancy and breastfeeding. All statistical evaluations will be carried out with regard to gender distribution.

Annex 1 References

Ahmed, Md Zahir, Oli Ahmed, Zhou Aibao, Sang Hanbin, Liu Siyu, and Akbaruddin Ahmad. 2020. 'Epidemic of COVID-19 in China and Associated Psychological Problems'. *Asian Journal of Psychiatry*. https://doi.org/10.1016/j.ajp.2020.102092.

Bajwah, S., A. Wilcock, R. Towers, M. Costantini, C. Bausewein, S. T. Simon, E. Bendstrup, et al. 2020. 'Managing the Supportive Care Needs of Those Affected by COVID-19'. *The European Respiratory Journal*. https://doi.org/10.1183/13993003.00815-2020.

Carfì, Angelo, Roberto Bernabei, and Francesco Landi. 2020. 'Persistent Symptoms in Patients after Acute COVID-19'. *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2020.12603.

Chen, Jun, Tangkai Qi, Li Liu, Yun Ling, Zhiping Qian, Tao Li, Feng Li, et al. 2020. 'Clinical Progression of Patients with COVID-19 in Shanghai, China'. *Journal of Infection*. https://doi.org/10.1016/j.jinf.2020.03.004.

Chen, Nanshan, Min Zhou, Xuan Dong, Jieming Qu, Fengyun Gong, Yang Han, Yang Qiu, et al. 2020. 'Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study'. *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30211-7.

Cirulli, Elizabeth T, Kelly M Schiabor, Barrett 1, Stephen Riffle, Alexandre Bolze, Iva Neveux, Shaun Dabe, et al. 2020. 'Long-Term COVID-19 Symptoms in a Large Unselected Population'. *MedRxiv*.

Galvan Casas, C, A Catala, G Carretero Hernandez, P Rodriguez-Jimenez, D Fernandez Nieto, A Rodriguez-Villa Lario, I Navarro Fernandez, et al. 2020. 'Classification of the Cutaneous Manifestations of COVID-19: A Rapid Prospective Nationwide Consensus Study in Spain with 375 Cases.' *The British Journal of Dermatology*. https://doi.org/10.1111/bjd.19163.

Holzner, Bernhard, Johannes M. Giesinger, Jakob Pinggera, Stefan Zugal, Felix Schöpf, Anne S. Oberguggenberger, Eva M. Gamper, August Zabernigg, Barbara Weber, and Gerhard Rumpold. 2012. 'The Computer-Based Health Evaluation Software (CHES): A Software for Electronic Patient-Reported Outcome Monitoring'. *BMC Medical Informatics and Decision Making*. https://doi.org/10.1186/1472-6947-12-126.

Hu, Katherine, Jay Patel, and Bhupendra C. Patel. 2020. *Ophthalmic Manifestations Of Coronavirus (COVID-19)*. *StatPearls*.

Kopel, Jonathan, Abhilash Perisetti, Ali Roghani, Muhammad Aziz, Mahesh Gajendran, and Hemant Goyal. 2020. 'Racial and Gender-Based Differences in COVID-19'. *Frontiers in Public Health*. https://doi.org/10.3389/fpubh.2020.00418.

Lai, Chih Cheng, Tzu Ping Shih, Wen Chien Ko, Hung Jen Tang, and Po Ren Hsueh. 2020. 'Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease-2019 (COVID-19): The Epidemic and the Challenges'. *International Journal of Antimicrobial Agents*. https://doi.org/10.1016/j.ijantimicag.2020.105924.

Lechien, Jerome R., Carlos M. Chiesa-Estomba, Daniele R. De Siati, Mihaela Horoi, Serge D. Le Bon,

Alexandra Rodriguez, Didier Dequanter, et al. 2020. 'Olfactory and Gustatory Dysfunctions as a Clinical Presentation of Mild-to-Moderate Forms of the Coronavirus Disease (COVID-19): A Multicenter European Study'. *European Archives of Oto-Rhino-Laryngology*. https://doi.org/10.1007/s00405-020-05965-1.

Li, Hui, Liang Liu, Dingyu Zhang, Jiuyang Xu, Huaping Dai, Nan Tang, Xiao Su, and Bin Cao. 2020. 'SARS-CoV-2 and Viral Sepsis: Observations and Hypotheses'. *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30920-X.

Li, J. 2020. 'Effect and Enlightenment of Rehabilitation Medicine in COVID-19 Management'. *European Journal of Physical & Rehabilitation Medicine*. https://doi.org/https://dx.doi.org/10.23736/S1973-9087.20.06292-9.

Li, Long quan, Tian Huang, Yong qing Wang, Zheng ping Wang, Yuan Liang, Tao bi Huang, Hui yun Zhang, Weiming Sun, and Yuping Wang. 2020. 'COVID-19 Patients' Clinical Characteristics, Discharge Rate, and Fatality Rate of Meta-Analysis'. *Journal of Medical Virology*. https://doi.org/10.1002/jmv.25757.

Mahase, Elisabeth. 2020a. 'Covid-19: What Do We Know about "Long Covid"?' *The BMJ*. https://doi.org/10.1136/bmj.m2815.

———. 2020b. 'Long Covid Could Be Four Different Syndromes, Review Suggests'. *BMJ (Clinical Research Ed.)*. https://doi.org/10.1136/bmj.m3981.

Mao, Ling, Huijuan Jin, Mengdie Wang, Yu Hu, Shengcai Chen, Quanwei He, Jiang Chang, et al. 2020. 'Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China'. *JAMA Neurology*. https://doi.org/10.1001/jamaneurol.2020.1127.

Menni, Cristina, Ana M. Valdes, Maxim B. Freidin, Carole H. Sudre, Long H. Nguyen, David A. Drew, Sajaysurya Ganesh, et al. 2020. 'Real-Time Tracking of Self-Reported Symptoms to Predict Potential COVID-19'. *Nature Medicine*. https://doi.org/10.1038/s41591-020-0916-2.

Mindell, Jennifer S., Simona Giampaoli, Antje Goesswald, Panagiotis Kamtsiuris, Charlotte Mann, Satu Männistö, Karen Morgan, Nicola J. Shelton, WM Monique Verschuren, and Hanna Tolonen. 2015. 'Sample Selection, Recruitment and Participation Rates in Health Examination Surveys in Europe - Experience from Seven National Surveys'. *BMC Medical Research Methodology*. https://doi.org/10.1186/s12874-015-0072-4.

Mo, Xiaoneng, Wenhua Jian, Zhuquan Su, Mu Chen, Hui Peng, Ping Peng, Chunliang Lei, Shiyue Li, Ruchong Chen, and Nanshan Zhong. 2020. 'Abnormal Pulmonary Function in COVID-19 Patients at Time of Hospital Discharge'. *The European Respiratory Journal*. https://doi.org/10.1183/13993003.01217-2020.

Moein, Shima T., Seyed M.R. Hashemian, Babak Mansourafshar, Ali Khorram-Tousi, Payam Tabarsi, and Richard L. Doty. 2020. 'Smell Dysfunction: A Biomarker for COVID-19'. *International Forum of Allergy & Rhinology*. https://doi.org/10.1002/alr.22587.

Ng, Siew C., and Herbert Tilg. 2020. 'COVID-19 and the Gastrointestinal Tract: More than Meets the Eye'. *Gut*. https://doi.org/10.1136/gutjnl-2020-321195.

Petrie, Joshua G., Caroline Cheng, Ryan E. Malosh, Jeffrey J. VanWormer, Brendan Flannery, Richard K. Zimmerman, Manjusha Gaglani, et al. 2015. 'Illness Severity and Work Productivity Loss among Working Adults with Medically Attended Acute Respiratory Illnesses: US Influenza Vaccine Effectiveness Network 2012-2013'. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/civ952.

Rello, Jordi, Enrico Storti, Mirko Belliato, and Ricardo Serrano. 2020. 'Clinical Phenotypes of SARS-CoV-2: Implications for Clinicians and Researchers'. *European Respiratory Journal*. https://doi.org/10.1183/13993003.01028-2020.

Richardson, Safiya, Jamie S. Hirsch, Mangala Narasimhan, James M. Crawford, Thomas McGinn, Karina W. Davidson, Douglas P. Barnaby, et al. 2020. 'Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area'. *JAMA*. https://doi.org/10.1001/jama.2020.6775.

Shi, Shaobo, Mu Qin, Bo Shen, Yuli Cai, Tao Liu, Fan Yang, Wei Gong, et al. 2020. 'Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China'. *JAMA Cardiology*. https://doi.org/10.1001/jamacardio.2020.0950.

Sudre, Carole H, Benjamin Murray, Thomas Varsavsky, Mark S Graham, Rose S Penfold, Ruth C Bowyer, Joan Capdevila Pujol, et al. 2020. 'Attributes and Predictors of Long-COVID: Analysis of COVID Cases and Their Symptoms 1 Collected by the Covid Symptoms Study App'. *MedRxiv*.

Tenforde, Mark W., Sara S. Kim, Christopher J. Lindsell, Erica Billig Rose, Nathan I. Shapiro, D. Clark Files, Kevin W. Gibbs, et al. 2020. 'Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020'. *MMWR. Morbidity and Mortality Weekly Report*. https://doi.org/10.15585/mmwr.mm6930e1.

Tourangeau, Roger, and Thomas J. Plewes. 2013. *Nonresponse in Social Science Surveys: A Research Agenda*. *Nonresponse in Social Science Surveys: A Research Agenda*. https://doi.org/10.17226/18293.

Troyer, Emily A., Jordan N. Kohn, and Suzi Hong. 2020. 'Are We Facing a Crashing Wave of Neuropsychiatric Sequelae of COVID-19? Neuropsychiatric Symptoms and Potential Immunologic Mechanisms'. *Brain, Behavior, and Immunity*. https://doi.org/10.1016/j.bbi.2020.04.027.

Wadhera, Rishi K., Priya Wadhera, Prakriti Gaba, Jose F. Figueroa, Karen E. Joynt Maddox, Robert W. Yeh, and Changyu Shen. 2020. 'Variation in COVID-19 Hospitalizations and Deaths Across New York City Boroughs'. *JAMA - Journal of the American Medical Association*. https://doi:10.1001/jama.2020.7197

Annex 2 Existing research facilities and employees, costs

General Information

Sponsor of the clinical trial	Medical University of Innsbruck Christoph-Probst-Platz 1, 6020 Innsbruck mui-sponsor@i-med.ac.at
Principal investigator Center A	Department of Internal Medicine II, Innsbruck Ao. Univ.-Prof. Dr. Judith Löffler-Ragg Anichstraße 35, 6020 Innsbruck judith.loeffler@i-med.ac.at
Principal investigator Center B	Institute of General Practice - LFHS Claudiana, Bozen Dr. Guliano Piccolori Lorenz-Böhler-Straße 13, I-39100 Bozen giuliano.piccoliori@am-mg.claudiana.bz.it

Table of Study Centers and investigators

Study Center A: **Medical University of Innsbruck, Christoph-Probst-Platz 1, 6020 Innsbruck**

Delegation	Name	Department/Address	E-Mail
Principal Investigator	Univ.-Prof. Dr. Judith Löffler-Ragg	University Clinic for Internal Medicine II, Anichstraße 35, 6020 Innsbruck	judith.loeffler@i-med.ac.at
Subinvestigators	Prim. Univ.-Prof. Dr. Günter Weiss[1] Univ.-Prof. Dr. Rosa Bellmann-Weiler[1] Priv.-Doz. Dr. Ivan Tancevski[1] Piotr Tymoszuk, PhD[1] Dr. Alex Pizzini[1] Dr. Thomas Sonnweber, PhD[1] Prim. Univ.-Prof. Dr. Stefan Kiechl[2] Priv.-Doz. Dr. Raimund Helbok[2] Dr. Verena Raß[2] Prim. Univ.-Prof. Dr. Barbara SpernerUnterweger[3] Priv.-Doz. Dr. Barbara Böckle[4] Univ.-Prof. Dr. Ursula Kiechl-Kohlendorfer[5] Dr. Herbert Bachler[6] Dr. Götz Nordmeyer[7]	[1]University Clinic for Internal Medicine II [2] University Clinic for Neurology [3] University Clinic for Psychiatry II [4] University Clinic for Dermatology [5] University Clinic for Paediatrics II Anichstraße 35, 6020 Innsbruck [6] Institute for General Medicine, Medical University Innsbruck, Innrain 52, 6020 Innsbruck [7] Landessanitätsdirektion Tirol, Boznerplatz 6, 6020 Innsbruck	Guetner.weiss@i-med.ac.at rosa.bellmann-weiler@i-med.ac.at ivan.tancevski@i-med.ac.at piotr.s.tymoszuk@gmail.com alex.pizzini@i-med.ac.at thomas.sonnweber@ i-med.ac.at stefan.kiechl@i-med.ac.at raimund.helbok@i-med.ac.at verena.rass@i-med.ac.at barbara.sperner-Unterweger@i-med.ac.at barbara.boeckle@i-med.ac.at ursula.kiechl-kohlendorfer@tirol-kliniken.at herbert.bachler@i-med.ac.at goetz.nordmeyer@tirol.gv.at
Sponsor	Medical University Innsbruck	Medical University Innsbruck Christoph-Probst-Platz 1, Innrain 52, 6020 Innsbruck	mui-sponsor@i-med.ac.at

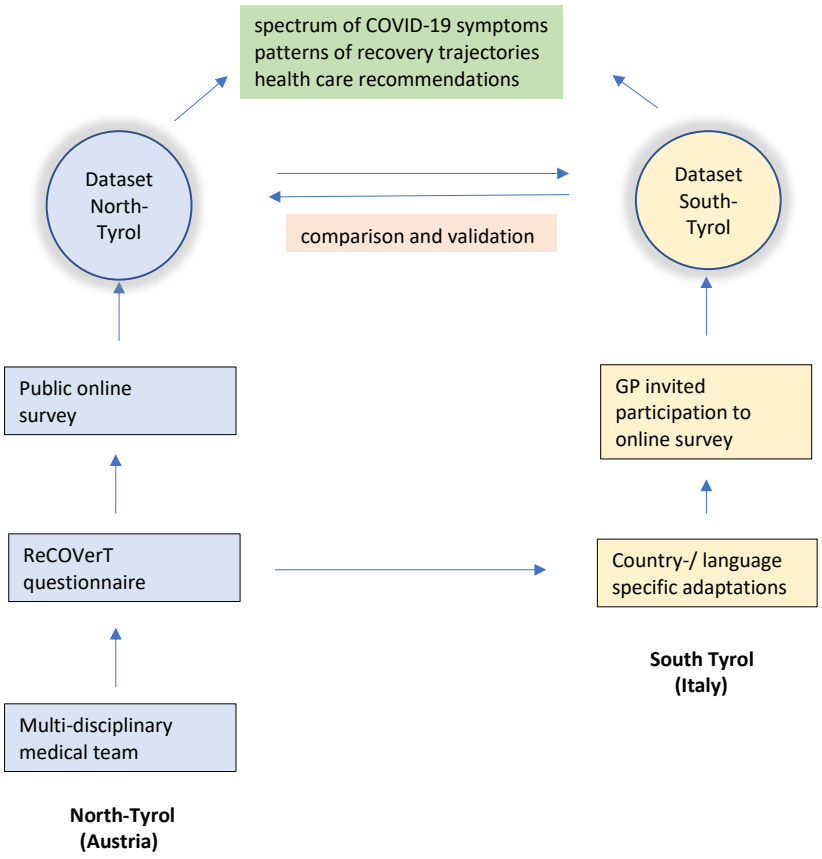
Study Center B:
Institute of General Practice – LFHS Claudiana, Lorenz-Böhler-Straße 13, 39100 Bozen-Bolzano (Italy)

Delegation	Name	Department/Address	E-Mail
Principal Investigator	Dr. Guiliano Piccoliori	Institute of General Practice, LFHS Claudiana, Lorenz-Böhler-Str. 13, 39100 Bozen-Bolzano	Giuliano.Piccoliori@am-mg.claudiana.bz.it
Subinvestigators	Dr. Dietmar Ausserhofer Dr. Angelika Mahlknecht Dr. Christian Wiedermann Dr. Adolf Engl	Institute of General Practice, LFHS Claudiana	dietmar.ausserhofer@claudiana.bz.it angelika.mahlknecht@am-mg.claudiana.bz.it christianjwiedermann@gmail.com adolf.engl@am-mg.claudiana.bz.it
Sponsor	College of Health Care-Professions Claudiana	Lorenz-Böhler-Straße 13, 39100 Bozen-Bolzano	direktion@claudiana.bz.it
Study coordination	Dr. Guiliano Piccoliori Dr. Dietmar Ausserhofer	Institute of Medicine, Lorenz-Böhler-Straße 13, 39100 Bozen-Bolzano	Giuliano.Piccoliori@am-mg.claudiana.bz.it dietmar.ausserhofer@claudiana.bz.it
Data management	Verena Barbieri	Institute of Medicine, Lorenz-Böhler-Straße 13, 39100 Bozen-Bolzano	verena.barbieri@gmx.net

Annex 3 Clinical Trial Synopsis

1) Title of Clinical Trial: **Health after COVID-19 in the European region North-Tyrol & South Tyrol (ReCOVerT)**

2) Graphical Overview:



3) Principal Investigator: ao Univ. Prof. Dr. Judith Löffler-Ragg on behalf of the ReCOVerT study team

4) Clinical Trial Type: Descriptive observational study applying a cross-sectional web-based survey

5) Objectives: Description and comparison of disease manifestation, convalescence and long-term consequences of SARS-CoV-2 positively tested probands in the European region North-Tyrol & South Tyrol. These data are expected to be hypothesis-generating for further analytical studies and health care planning.

6) Intervention: Epidemiological research by means of an anonymised, multi-item cross-sectional survey with voluntary participation in the two European COVID-19 hotspots.

7) Key inclusion and exclusion criteria: Individuals resident in North-Tyrol or South-Tyrol with confirmed expired SARS-CoV-2 Infection. Children are excluded from the examination. Further country specific different inclusion criteria regarding age and definition of recovery are specified within the proposal.

8) Primary and Secondary Endpoint(s):

Primary endpoint:

- Percentage of patients who recovered, defined as being without symptoms four weeks after onset of COVID-19
- Identification of symptom patterns of acute COVID-19 predicting protracted recovery

Secondary endpoints:

- Percentage of patients who recovered, defined as being without symptoms three or six months after onset of COVID-19
- Type and number of symptoms during the acute infection
- Individual recovery trajectories (type and duration of symptoms persisting over time)
- General health status
- Respiratory health status
- Neurologic health status
- Mental health status after COVID-19
- Psychosocial health status
- Rehabilitation needs

9) Sample Size, Statistical Analyses, Power Calculation:

Sample size estimation to analyse the primary hypothesis in the two independent survey cohorts suggests a sample size of at least of 572 patients in South-Tyrol, respectively 671 patients in North-Tyrol. Based on the observational design descriptive statistics will be applied.

10) Trial Duration: 19 months (April 2020 to October 2021)

11) Participating Centres:
Medical University of Innsbruck, Austria & Institute of General Practice, LFHS Claudiana, Bolzano, Italy