Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Short title: Immunocompromised Swiss Cohorts Based Trial Platform

Acronym: COVERALL (COrona VaccinE tRiAL pLatform)

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Category A (reassessment will be done in separate sub-protocols)
Study Registration:	Clinicaltrials.gov: NCT04805125Planned: kofam
Study Identifier:	COVERALL
Sponsor, Sponsor-Investigator or Principal Investigator:	University Hospital Basel Prof. Heiner C. Bucher MD MPH Basel Institute for Clinical Epidemiology & Biostatistics University Hospital Basel Spitalstrasse 12 4056 Basel Switzerland Phone: +41 (0)61 328 61 01 Email: heiner.bucher@usb.ch
Investigational Product:	In Switzerland approved SARS-CoV-2 vaccines (i.e. vaccines with market authorisation by Swissmedic). Investigated vaccines are specified in, a separate sub-protocol and submitted to the EKNZ via BASEC.
Protocol Version and Date:	**Version 2.1; 07.04.2021**

CONFIDENTIAL

The information contained in this document is explicitly not confidential. We will make all study protocols (including master protocol, sub-protocols, as well as amendments) publicly available on Open Science Framework (https://osf.io/)

Signature pages

Sponsor-Investigator

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	University Hospital Basel Basel Institute for Clinical Epidemiology & Biostatistics Spitalstrasse 12 4031 Basel
Sponsor-Investigator	Prof. Heiner C. Bucher

Basel 10.3.2021

Place/Date

Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

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Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	University Hospital Basel Dep. of Infectious Diseases and Hospital Hygiene Petersgraben 4 4031 Basel
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Basel, 09.03.21

Place/Date

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Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	Universitätsspital Zürich
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Zürich, 8 March 2021 — H. Günthard

Place/Date — Signature

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Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	Universitätsklinik für Infektiologie Freiburgstrasse 16p, Haus 5, Stock E 3010 Bern
Principal investigator	Dr. Anna Lena Eichenberger

Bern, 8/02/24

Place/Date

Signature

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Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	Universitätsspital Zürich Klinik für Pneumologie Rämistrasse 100 8091 Zürich
Principal investigator	PD Dr. Macé Schuurmans

Zürich, 11/2/2021

Place/Date

Signature

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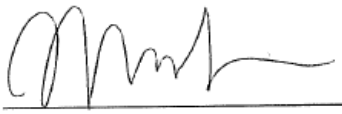
Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	CHUV Service des maladies infectieuses Rue du Bugnon 46 1011 Lausanne
Principal investigator	Prof. Oriol Manuel

Lausanne, 8.2.2021

Place/Date



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Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	CHUV Service des maladies infectieuses Rue du Bugnon 46 1011 Lausanne
Principal investigator	Prof. Matthias Cavassini

Lausanne, le 8.02.2021 _____

Place/Date Signature

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Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	Universitätsspital Zürich Klinik für Nephrologie Rämistrasse 100 8091 Zürich
Principal investigator	Prof. Thomas Müller

Zürich, 08/02/21 _____ _____

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Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	Universitätsspital Basel Pneumologie Petersgraben 4 4051 Basel
Principal investigator	Prof. Michael Tamm

8/2/2021, Basel

Place/Date

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Clinical Study Master-protocol

Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform

Site	Universitätsspital Basel Transplantationsimmunologie & Nephrologie Petersgraben 4 4051 Basel
Principal investigator	Prof. Michael Dickenmann

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Place/Date Signature

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STUDY SYNOPSIS

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Study Title:	Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of an Swiss Cohorts Based Trial Platform
Short Title / Study ID:	Immunocompromised Swiss Cohorts Based Trial Platform
Protocol Version and Date:	Version 2.0; 23 .01.2021
Trial registration:	Clinicaltrials.gov: NCT04805125Planned: kofam
Study category and Rationale	We plan to set up a flexible trial platform using two existing national cohorts of immunocompromised patients (i.e. Swiss HIV Cohort Study [SHCS] and Swiss Transplant Cohort Study [STCS]) to assess the comparative effectiveness and safety of approved SARS-CoV-2 vaccines in immunocompromised patients. Nesting this trial into cohorts with highly standardized data collection allows for a rapid, efficient and cost-saving trial conduct while addressing a highly relevant research question. With the current pandemic situation of SARS-CoV-2 infection, our focus is on vaccines in immunocompromised hosts. We will test this platform in the frame of an exploratory pilot trial and we will set-up a framework to conduct a larger, flexible, randomized controlled trial (RCT) to test approved SARS-CoV-2 vaccines to prevent SARS-CoV-2 infections. The pilot trial will be a category A trial as all used vaccines will be approved in Switzerland and entails only minimal risks. The actual vaccines tested, including more specific inclusion and exclusion criteria and dosing will be defined in separate sub-protocols that will be submitted as soon as vaccines are licensed in Switzerland.
Clinical Phase:	Phase 3/4

Background and Rationale:	A new highly contagious corona virus SARS-CoV-2 has emerged in late 2019 in Wuhan, China, and caused in a two month period a pandemic with the highest disease burden in elderly and people with pre-existing medical conditions. In a situation with no known therapy against SARS-CoV-2 clinical research in Switzerland was ill-prepared at the beginning of the pandemic for launching clinical trials for the rapid evaluation of investigative drugs with postulated in vitro activities against SARS-CoV-2. Use of routinely collected data for nesting trials into cohort studies with highly standardized data collection systems and platform trials allows for rapid patient recruitment and efficient and cost-saving data collection for the simultaneous evaluation of several treatment options, features which can expedite trial protocol development and trial implementation in an epidemic situation. The advantage of using the existing infrastructure of two well-established cohorts is that eligible patients most urgently at need for vaccines or therapies can be more rapidly identified and recruited to trials during regular cohort visits, or by calls. Due to rigorous follow-up monitoring and collection of high-quality phenotypic data the cohort data can be used to define trial baseline data but also for outcome assessment for those parameters that are routinely collected like for example hospitalisations, pneumonia, or death. The use of highly standardized routinely collected data for conducting intervention trials is a highly efficient and economic approach for trial conduct as exemplified by previous groups. Furthermore, a well-established trial platform would allow us to react quickly in case of any future outbreak, meaning that fewer hurdles need to be overcome to implement a clinical trial. At present (December 08 2020) Switzerland has still around 4000 new SARS-CoV-2 infections per day. Hospitalisations and deaths due to SARS-CoV-2 are high with 18 hospitalisations per 100`000 inhabitants and 11 per 100'000 deaths and the reproduction rate is still around 1 (https://www.covid19.admin.ch/de/overview/hospitalisationen?detTime=14d). It remains unclear whether the current reproduction rate of SARS-CoV-2 can be further lowered and kept during this winter season. According to the University of Oxford (November 25, 2020, https://www.covid-19vaccinetracker.org/) 40 vaccines against SARS-CoV-2 are in clinical evaluation, and of those, 10 vaccines are in phase III (including one non-replicating viral vector, three inactivated vaccines, one LNP-encapsulated mRNA, and one 3 LNP-mRNAs) and 237 candidate vaccines are under preclinical investigation. Two vector based mRNA vaccines by Pfizer/BioNTech and Moderna have been approved December 19, 2020 and January 12, 2021 by Swissmedic and vaccination programs start to be rolled out in Switzerland. The Swiss Federal Government has acquired large stocks of both vaccines. These vaccines and others to come use new vector based vaccine strategies that have never been used in humans. In particular, safety and efficacy data in immune compromised patients is only existing in a very limited amount or not at all. Therefore, it is paramount to compare new emerging vaccines for safety and efficacy in those individuals who are at increased risk of complicated Sars-CoV-2 infection and are likely to have reduced vaccine induced immunity like elderly and immune compromised patients. The here presented revised master protocol describes the set-up of the trial platform which is nested into two cohorts and the annexed first sub-study protocol details the pilot RCT which intends to compare the immune response, clinical effectiveness and safety of the first two in Switzerland approved mRNA vaccines against Sars-Cov_2 in immunocompromised patients. We had submitted the master protocol of the trial platform December 15, 2020 to the Leitethikkommission EKZN without a sub-study protocol as at that time point no vaccine had achieved market authorisation by Swissmedic in order to start a potential trial in a timely manner. The pilot study will primarily assess the functionality of the trial platform and early immunogenicity, efficacy and safety data. At a later stage, the platform might also be used to enlarge the pilot trial or to develop sub-protocols to deal with patients with no or insufficient immune response to Sars-CoV-2 vaccines.

Objective(s):	The overall objective is to use existing resources from two established national cohorts (i.e. SHCS and STCS) to build a flexible trial platform and to test this platform in the frame of a randomised pilot trial by comparing induced immunity of the two first vaccines that are licensed in Switzerland to prevent SARS-CoV-2 infections and related complications in immunocompromised patients.

Outcome(s):	For the conduct of this pilot trial we will assess the feasibility of conducting a RCT in Switzerland based on our newly developed platform. **Specific endpoints related to trial conduct feasibility** within the cohort and trial platform infrastructure will be the following: • Duration of RCT set up (i.e. time from deciding which interventions will be tested until the first patient is randomised). • Time of patient recruitment (i.e. from activation of first study site until (i) 40 patients and (ii) 380 patients are randomised) • Patient consent rate (i.e. proportion of patients giving informed consent out of approached eligible patients) • Proportion of missing data for all baseline variables from routinely collected cohort data (baseline variables are listed under "Measurements and procedures") • Proportion of missing data for all clinical outcomes from routinely collected cohort data and outcome data that is collected in the trial platform (clinical outcomes are listed below) **Specific SARS-CoV-2 related outcomes** will be collected during the sub-study pilot phase. These will be the following: **Immunological outcome (primary endpoint) :** We will measure SARS-CoV-2–specific antibodies and titers with established assays, in all participants at three months after vaccination. We will use a commercial pan-IgG antibody assay against the receptor binding domain (RBD) against the nP and spike 1 subunits and an in-house assay developed by the Institute of Medical Virology, University of Zurich which can detect multiple viral epitopes. **Clinical outcomes (secondary endpoints):** The clinical effectiveness endpoints are (according to FDA recommendations for phase III Covid-19 vaccine licensing trials) the following: - Newly PCR-confirmed asymptomatic Covid-19 infection (identified by the presence of anti–SARS-CoV-2 nucleocapsid antibodies, or SARS-CoV-" PCR or rapid antigen test) and no related symptoms [(i.e. fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose nausea or vomiting, and diarrhea]) at any time points within 48 weeks follow-up - Newly PCR-confirmed symptomatic Covid-19 infection with at least one of the following symptoms (i.e. fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose nausea or vomiting, and diarrhea) within 48 week follow-up - Severe COVID-19 infection with respiratory failure, evidence of shock (as diagnosed by a treating physician), clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death within 48 week follow-up. - Covid-19 burden of diseases (BOD), a composite of the above endpoints. The BOD will be scored as by using 0 for no COVID-19, 1 for non-severe COVID-19, and 2 for severe COVID-19. An additional clinical effectiveness endpoint is patient reported symptomatic or symptomatic infections of household members. All clinical outcomes will be measured in the trial database during a follow-up period of 12 months after vaccination. **Safety outcomes:** Collection of solicited local and systemic adverse events will for feasibility reasons be reduced to: • Any local symptom (redness or swelling or prolonged pain at injection side) limiting the continuation of normal daily activities during the first 7 days after vaccination • Any systemic symptom (fever, generalized muscle or joint pain) limiting the continuation of normal daily activities during the first 7 days after vaccination

	• Any vaccine related symptom leading to contacting a physician during the first 7 days after vaccination .
Study design:	Cohort embedded platform with a first sub-study pilot trial of two arms comparing licensed vaccines against SARS-CoV-2. The platform design allows to expand the pilot trial into a larger trial by sub-protocols to add or drop vaccine arms or to add further sub-protocols for re-randomization of patients with no immune response to a vaccine booster or new vaccines The interventions are further specified in the separate sub-protocol.
Inclusion / Exclusion criteria:	Inclusion criteria - Aged ≥18 years - Patients registered with informed consent from participating cohorts - Additional consent for participation in the specific sub-protocol Exclusion criteria - Acute symptomatic SARS-CoV-2 infection, influenza or other acute respiratory tract infection -Known allergy or contra-indications for vaccines or any vaccine components - Any emergency condition requiring immediate hospitalization for any condition Inclusion and exclusion criteria (e.g. pregnancy) are specified further in the separate sub-protocol.

Measurements and procedures:	Baseline characteristics will be measured and used from routinely collected cohort data. Baseline data from SHCS patients will include the following: Age, sex, education, working status, co-morbities diabetes mellitus, hypertension, dyslipidemia, coronary heart diseases angioplasties, bypass surgery and strokes, body mass index, depression, smoking, alcohol and illicit drug use, current antiretroviral therapy and any co-medication, first HIV antibody test or inclusion into cohort, CD4 cell nadir, latest CD4 cell count & HI viral load, glomerular filtration rate, hepatitis C virus (HCV) and chronic hepatitis B virus (HBV) infection, hematogram and blood chemistry including GFR, contact with a person with a documented SARS-CoV-2 infection, past documented SARS-CoV-2 infection by either SARS-CoV-2 PCR or antibodies (IgG). Baseline data from STCS patients will include the following: Age, sex, ethnicity, history of transplantation, organ-specific pre-transplant history, hospitalization duration for the actual transplantation, patient medical history (cardiopulmonary diseases, metabolic diseases, endocrine diseases, kidney diseases, history of cancer and other events and diseases), history of infectious diseases, infectious diseases at baseline (viral, bacterial, fungal, parasite, unindentified), immunosuppressive treatment, lab data (chemistry and hematology), immunology, serology (HBV, HCV, CMV, HIV, EBV, Toxo, Tpha, HSV, VZV), HLA typing, allograft biopsy (date and ID), drugs (induction, maintenance of immunosuppression and infectious diseases prophylaxis, plus other important treatments), education, work status , smoking history, drug addiction, depression. The baseline data will also serve for the identification of eligible patients who are at highest risk of complications from SARS-CoV-2 infection. Clinical trial endpoints and serious adverse events will be continuously collected by clinicians of participating clinical cohort centres and entered by the local clinicians and local cohort data managers into the clinical outcome trial platform database. The data centres and local data managers of the SHCS and STCS will manage and control the trial platform database and will be responsible for data monitoring. The cohort data centres will check for consistency of all outcome data that is entered in parallel into the routine cohort database and into the trial outcome database (e.g. clinical information on any or SARS-CoV-2 related hospitalization and exact reasons of death).
Study Product / Intervention:	We will primarily assess the feasibility of conducting a randomised vaccine trial that is nested in two cohorts in Switzerland with the purpose to measure the specific endpoints related to trial conduct feasibility, and the immunological and clinical endpoints in regard to vaccine efficacy and safety.. The first in Switzerland approved SARS-CoV-2 vaccine will constitute the trial study intervention (and will be described in a separate sub-protocol following the licensing of the vaccines).
Control Intervention (if applicable):	The second approved SARS-CoV-2 vaccine will constitute the trial control group.
Number of Participants with Rationale:	To pilot the trial and test the functionality of the trial platform we plan to enrol 380 patients over 3 months in 4 cohort centers (with multiple transplantation programs for the STCS).
Study Duration:	Vaccines by Pfizer / BioNTech and Moderna have been approved December 19, 2020 and January 12, 2021.Extended follow-up for patient reported outcomes that are collected within the ongoing cohort data collection is feasible and will be done for 48 weeks.

Study Schedule:	First-patient-in (planned): March 2021 Last-patient-in (planned): July 2021 Last patient out (planned 48 week visit): July 2022 We anticipate that 3 months of recruitment will be sufficient for a pilot study focusing on the specific endpoints All follow-ups will be conducted in the frame of the ongoing cohort studies (i.e. SHCS and STCS).

Investigator(s):	Principal investigator: Prof. Heiner C. Bucher MD MPH Basel Institute for Clinical Epidemiology & Biostatistics Universitätsspital Basel und Universität Basel Spitalstrasse 12 4031 Basel, Switzerland Phone: +41 (0)61 328 61 01 Email: heiner.bucher@usb.ch Investigators: Benjamin Speich, PhD Basel Institute for Clinical Epidemiology & Biostatistics Universitätsspital Basel und Universität Basel Spitalstrasse 12 4031 Basel Email: benjamin.speich@usb.ch PD Michael Koller, MD MSc Transplantationsimmunologie und Nephrologie, Datenzentrum Swiss Transplant Cohort Study Universitätsspital Basel und Universität Basel Spitalstrasse 12 4031 Basel Switzerland Email: Michael.koller@usb.ch Prof. Nicolas Müller MD Klinik für Infektionskrankheiten und Spitalhygiene Universitätsspital Zürich und Universität Zürich Rämistrasse 100 8091 Zürich Email: nicolas.mueller@usz.ch Prof. Huldyrch Günthard MD PhD Universitätsspital Zürich und Universität Zürich Rämistrasse 100 8091 Zürich Email: huldrych.guenthard@usz.ch Spitalstrasse 12 4056 Basel Switzerland Prof. Andri Rauch MD PhD Inselspital, Universitätsspital Bern Freiburgstr. 16p 3010 Bern

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Study Centre(s):	A multi-center study of 4 study centres of the SHCS and STCS (with multiple transplantation programs at centers within the STCS).
Statistical Considerations:	All specified outcomes will be descriptively summarized for the two vaccine arms, as well as for important subgroups. This is a pilot study. Once relevant sub-group results of the phase III licensing vaccine trials pertinent to patients of this trial are published we will explore whether powering the trial for non-inferiority of the second licensed vaccine compared to the first licensed vaccine is feasible.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
BOD	Burden of disease
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
COVID	Corona virus diseases
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
CONSORT	Consolidated Standards of Reporting Trials
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
FDA	Food and drug administration
GCP	Good Clinical Practice
GMT	Geometric mean titers
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HIV	Human Immunodeficiency Virus
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
MD	Medical Device
MedDO	Medical Device Ordinance *(in German: MepV, in French: ODim)*
PI	Principal Investigator
RBD	Receptor binding domain
RECORD	REporting of studies Conducted using Observational Routinely-collected Data
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDV	Source Data Verification
SHCS	Swiss HIV Cohort Study
SOP	Standard Operating Procedure
SPC	Summary of product characteristics

SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STCS	Swiss Transplant Cohort Study
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

STUDY SCHEDULE

	STUDY PERIOD				
	Eligibility	**Enrolment, randomisation & vaccination**	**Post-randomisation**		
TIMEPOINT	**Approximately -12 weeks**	**Day 0**	**Week 12 (±7 days)**	**Week 48 (±7 days)**	**Continuous follow-up in the frame of the cohort**
ENROLMENT:					
Eligibility screen[a]	X[a]				
Eligibility assessment	X				
Informed consent		X[a]			
Allocation		X[b]			
INTERVENTIONS:					
Group A: Vaccine 1		X			
Group B: Vaccine 2		X			
ASSESSMENTS:					
BASELINE VARIABLES (will be exported from routine cohort data) Baseline blood sample	X				
IGG neutralizing antibodies post randomisation but prior to vaccination		X			
CLINICAL OUTCOMES:	X[e]	X[e]			
- Immune response IgG neutralizing antibodies		X	x[c]		
- Newly confirmed asymptomatic SARS-CoV-2 infection			x[c]	x[c,d]	x[d]
-Newly confirmed symptomatic SARS-CoV-2 infection			x[c]	x[c,d]	x[d]
- Severe COVID-19 infection with respiratory failure, evidence of shock, organ failure, admission to ICU, or death			x[c]	x[c,d]	x[d]
- Adverse events from vaccines			x[c]		
-Serious adverse events			x[c]	x[c,d]	x[d]
- PCR confirmed symptomatic infections of household members			x[c]	x[c,d]	x[d]

[a]Continuous assessment and selection from routinely collected cohort data

[b]Enrolment and concealed allocation of patients with informed consent will be performed during the same visit when the study is explained to the patient, or, if preferred, during a separate arranged study visit.

[c]Assessed in separate data entry form for the trial

[d] Assessed by routine data collection from cohort database

[e]Baseline blood samples will be taken from previous cohort visits (no longer than 6 months) or during cohort and randomisation visits at day 0.

1. STUDY ADMINISTRATIVE STRUCTURE

A safety committee consisting of two infectiologists not otherwise involved in the trial and a biostatistician will be formed to oversee patient enrolment and efficacy and safety issues in regard to vaccines used during the pilot trial.

1.1 Sponsor-Investigator

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1.6 Monitoring institution

No external monitoring is planned during the pilot study. Central monitoring of data entry into the trial platform and cohort database will be done within the routine procedures by the local cohort data managers and the biostatistician responsible for the sub-study pilot trial.

1.7 Data Safety Monitoring Committee

An independent data safety monitoring board (IDSMB) will be established which will be advisory to the Trial Committee that constitutes of the PI and the co-investigators. The IDSMB will be regularly informed by the primary investigator, the primary co-investigator, and the trial biostatistician on any safety aspects and on serious adverse events from vaccinations from the first sub-study protocol.

For future sub-study protocols that may involve adding or dropping of study arms based on results from interim analyses a detailed action plan, an analysis with stopping rules for harm, benefit and futility will be established. The IDSMB has to decide which data from the interim analyses has to be shared with the trial committee. Prior to a (first) interim analysis the IDSM and the Trial Committee will meet to review potential scenarios following the interim analysis and will agree on the communication prior and after the interim analysis to trial sites and study participants. The following independent scientists have

agreed to be part of the IDSMB:

- Tracy Glass, PD, PhD; Biostatistician at the Swiss Tropical and Public Health Institute (Swiss TPH)
- Prof. Andreas Widmer, former vice head of department for Infectious Diseases & Hospital Epidemiology at the University Hospital Basel
- Prof. Pietro Vernazza, Head of the department for Infectious Diseases, Kantonal Hospital St. Gallen.

1.8 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

1.9 Authors contributions

Heiner Bucher (HB); Michael Koller (MK); Matthias Briel (MB); Lars Hemkens (LG); Frédérique Chammartin (FC); and Benjamin Speich (BS) designed the study. Nicolas Müller (NM); Huldyrch Günthard (HG); Andri Rauch (AR); Daniel Smith (DS) and Katharina Kusejko (KK) gave scientific input. BS and HB wrote the first draft of the protocol. All authors critically revised and approved the final version of the study protocol. HB acquired funding for the trial.

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the master protocol, as well as the sub-protocol (which defines the actual intervention plus additional inclusion and exclusion criteria) will be submitted to a properly constituted Competent Ethics Committee (CEC). The decision of the CEC will be made in writing to the Sponsor-Investigator before commencement of this study. The study will not start recruiting patients before receiving ethical approval. We have contacted Swissmedic for a “Pre-assessment clinical trial with complex design”. Swissmedic rated a pilot trial of licensed vaccines as category A study with no further need of approval from Swissmedic (see separately submitted document: Email exchange with Swissmedic). All sub-study protocol and changes to the master-protocol are subject to additional ethical approval.

2.1 Study registration

The trial platform and sub-studies protocols is registered with the U.S. National Institutes of Health (www.clinicaltrials.gov) under NCT04805125. The trial platform and sub-studies protocols will also be registered with the Koordinationsstelle Forschung am Mensch (kofam).

2.2 Categorisation of study

Category A. This study will use vaccines against SARS-CoV-2, which have been licensed by Swissmedic in accordance with the prescribing information approved by Swissmedic and which - by guidelines from the BAG and Kommission für Impffragen - may be used in immune suppressed individuals when considering the individual benefits and risks.

2.3 Competent Ethics Committee (CEC)

The Principle/Sponsor Investigator will ensure that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the study.

Changes of the protocol will be implemented, unless to prevent immediate danger, without prior Sponsor and Ethics committee approval.

Premature study end or interruption of sub-study protocols will be reported within 15 days. The regular end of the sub-study protocol and the trial platform is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

To obtain approval from Swissmedic is not planned as this will be a Category A study (see also “2. Ethical and regulatory aspects” and “2.2. Categorisation of study”).

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki (1), the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority’s requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

All staff involved in the trial will have to fulfil requirements in regard to training, data management and data analysis.

Writing of protocol and final manuscripts will be in adherence with reporting standards of SPIRIT (2),

CONSORT (3) and RECORD (4).

2.6 Declaration of interest

This investigator-initiated trial will be conducted with public support by Swiss National Science Foundation grant #177499 (Swiss HIV Cohort Study), grant # 31CA30_196245 (COVID-19 call) and 33CS30_134267/1 (Swiss Transplant Cohort Study). The sponsor of this trial is the University Hospital of Basel. All participating investigators and authors declare no conflict of interests.

2.7 Patient Information and Informed Consent

Cohort participants will be contacted by the local centers and invited to get an appointment at the site vaccination center for a vaccination against SARS-CoV-2 or get information about vaccines and the trial during cohort visits. When a potentially eligible patient is visiting a local cohort centre, the investigators will explain the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. Only patients who do want to get vaccinated independently of the trial will be approached for trial participation. Patients will have sufficient time to ask questions and to consent to trial participation. Patients are allowed to consider trial participation at a sub-sequent visit and to have time to consider trial participation.

Participants have already provided written informed consent that their data, stored plasma and blood cell samples that are routinely collected within the Swiss HIV Cohort Study and the Swiss Transplant Cohort Study are used by authorised researchers of both cohorts other than their treating physician in the frame of the ongoing cohort studies.

All participants for the study will be provided with a participant information sheet which can be handed out to patients during or prior to cohort visits or by mailing. The consent form describing the trial and providing sufficient information for participants to make an informed decision about their participation in the study will be given to patients during cohort visits. The patient information sheet as well as the consent sheet will be submitted to the CEC for review and approval. Based on the patient's preferences the random assignment will be done during the same visit or at a later time point (i.e. within the next 14 days).

The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his/her designee) at the same time as the participant signs, and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study (including sub-studies) is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the trial platform and/or a sub-study prematurely according to certain circumstances, for example:

- ethical concerns,

- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- evidence of harm from investigated vaccines

2.10 Protocol amendments

Substantial amendments are only implemented after being discussed amongst the study investigators and after approval of the CEC. The start or closure of a sub-study will be added to the master-protocol as an amendment and are reported to the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

All minor amendments that have no direct effect on the study conduct and are of primarily administrative nature will be recorded. These changes will be reported to the CEC on the Principal Investigator discretion. All changes will be documented in the final results publication of the pilot study.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

A new highly contagious corona virus SARS-CoV-2 has emerged in late 2019 in Wuhan, China, and caused in a two months period a pandemic with the highest disease burden in elderly and people with pre-existing medical conditions (5-7). HIV positive individuals are suffering from multiple comorbidities in particular cardiovascular disease and diabetes due to aging, risk factors for chronic diseases and life style factors, which put them at higher risk of complicated Sars-CoV-2 infection (8). Whether poor immune recovery in the presence of antiretroviral therapy is associated with increased risk of Sars-CoV-2 infection and complicated infection is unclear. End of October 2020 100 Sars-CoV-2 infections 22 hospitalisations and 2 deaths due to Sars-CoV-2 were noted in the SHCS.

Likewise solid organ transplanted patients are suffering from multiple chronic conditions like cardiovascular disease and diabetes and treated with immunosuppressive drugs putting them at risk of multiple infections and severe infection related complications.

On the April 3rd 2020 21 patients had a documented Covid-19 infection. Twenty patients were hospitalized, 5 were transferred to the ICU, 4 of them required mechanical ventilation and two renal transplant recipients died. An update of the number of confirmed SARS-CoV-2 infections by end of August revealed 30 confirmed cases, of which 24 were hospitalized and 6 patients had died.

In a situation with no known therapy against SARS-CoV-2 clinical research in Switzerland was ill-prepared at the beginning of the pandemic for launching clinical trials for the rapid evaluation of investigative drugs with postulated in vitro activities against SARS-CoV-2. Use of routinely collected data for nesting trials into cohort studies with highly standardized data collection systems and platform trial design allow rapid patient recruitment and efficient and cost-saving data collection for the simultaneous evaluation of several treatment options, features which can expedite trial protocol development and trial implementation in an epidemic situation (9-13).

The advantage of using the existing infrastructure of two well-established cohorts is that the processes of rigorous follow-up monitoring and collection of high-quality phenotype data is already well established and will be performed entirely within the existing cohorts (14, 15). The use of highly standardized routinely collected data for conducting intervention trials is a highly efficient and economic approach for trial conduct as exemplified by previous groups. Furthermore, a well established trial platform would allow us to react quickly in case of any future outbreak, meaning that fewer hurdles need to be overcome to implement a clinical trial.

At present (December 08 2020) Switzerland has still around 4000 new SARS-CoV-2 infections per day (16). Hospitalisations and deaths due to SARS-CoV-2 are high with 18 hospitalisations per 100`000 inhabitants and 11 per 100'000 deaths and the reproduction rate is still around 1 (16). It remains unclear whether the reproduction rate of SARS-CoV-2 can be constantly be kept below 1 during the upcoming winter season.

According to the Oxford University based vaccines tracker (237 vaccines against Sars-coV-2 are in development and 38 are actually undergoing clinical testing (17). Of those 10 vaccines are in phase III (including one non-replicating viral vector, three inactivated vaccines, one LNP-encapsulated mRNA, and one 3 LNP-mRNAs).

For example, in the UK, the first vaccine by Pfizer was already approved and others are expected to be evaluated soon (18). Hence, it is possible, that one or more SARS-COV-2 vaccines are approved in Switzerland within the next weeks. This trial platform with the corresponding master protocol will outline a pilot RCT to test approved vaccine candidates in immunocompromised patients. The platform is developed within the infrastructure of two well-established cohorts in Switzerland, the Swiss HIV Cohort Study (14) and the Swiss Transplant Cohort Study (15) and allows to nest trials into the existing cohort data infrastructure. This allows for more efficient patient recruitment, and the use of cohort baseline data and for the collection of long-term patient relevant outcome data by taking advantage of the routinely collected clinical outcome data. At present, it appears most likely that vaccines by BioNTech/Pfizer, Moderna and Oxford University/Astra Zeneca will first FDA emergency act approval and accelerated approval by Swissmedic as the Swiss government has already acquired large stocks of these vaccines.

The trial platform will be ready (before vaccine candidates are available in Switzerland (i.e. vaccines with market authorisation by Swissmedic). Therefore, we intend to have the trial platform approved by ethics committee prior to authorisation of vaccines in order to accelerate the preparation of the trial. The specific vaccines interventions will be approved by supplementary trial sub-protocols. These procedures have been approved by our application to Swissmedic which has created a review process for drug approval trials with complicated design. This will allow us to start a potential trial in a timely manner when vaccines are available (i.e. after approval of specific sub-protocols). The pilot study will assess the functionality of the trial platform and the comparative effectiveness in terms of antibody response, clinical and safety outcomes of the first two approved vaccines against Sars-CoV-2 At a later stage, the platform can serve for a larger comparative vaccine trial of or can be enriched by new study protocol that investigate the comparative effectiveness for example in vaccinated individuals in the cohort that did not achieve an immune response after the first vaccine.

3.2 Investigational Product (treatment, device) and Indication

Only SARS-CoV-2 vaccines which have market authorisation by Swissmedic will be selected. As soon as two potential investigational products are identified, they will be described in detail in a separate sub-protocol which will also be submitted to the CEC for review and approval.

3.3 Preclinical Evidence

Not applicable as the intervention is not yet selected. As soon as a potential investigational product is identified, it will be described in detail in a separate sub-protocol which will also be submitted to the CEC for review and approval.

3.4 Clinical Evidence to Date

Not applicable as the intervention is not yet selected. As soon as a potential investigational product is identified, it will be described in detail in a separate sub-protocol which will also be submitted to the CEC for review and approval.

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

We will use the exact same vaccine dose or doses as described in the Swiss market authorisation by Swissmedic.

3.6 Explanation for choice of comparator (or placebo)

The first two vaccines (Pfizer/BioNTech and Moderna) against Sars-CoV-2 have been licensed in Switzerland on December 21, 2020 and January 12, 2021. For logistic reasons not all patients can be vaccinated immediately after licensing. Some vaccines require storage at low temperature (-60^0 C) which makes vaccination at centres necessary. Therefore, it is unlikely that the vast majority from the two cohorts will be routinely vaccinated during the time when only one vaccine is available. As soon as a second vaccine is approved in Switzerland, we will start our pilot randomised controlled trial, using dynamic randomisation technique of minimisation to minimise imbalance allocation to one of two active vaccines.

3.7 Risks / Benefits

Any adverse events will be collected within the trial database which is linked to the two cohort databases. Severely immunocompromised patients with a chronic HIV infection or solid organ transplant and immunosuppressive drug intake are at higher risk of complications from SARS-CoV-2 infection. Therefore, we anticipate that this population is very likely to profit from a SARS-COV-2 vaccine. No safety or efficacy data of any vaccine from these populations is currently available, and it is unknown whether vaccine related complications in these populations might be increased.

3.8 Justification of choice of study population

According to the Swiss Federal Office of Public Health, individuals with a condition or therapies that weaken the immune system are at especially high risk to have a severe case of COVID-19 disease (19). Hence, according to the guidelines from the BAG and Kommission für Impffragen the vaccines may be used in immune suppressed individuals when considering the individual benefits and risks in Switzerland, we have two national cohorts including such patients, namely the Swiss HIV cohort study (SHCS) (14) and the Swiss Transplant Cohort Study (STCS) (15). Combining these two cohorts in the frame of an established trial platform is an excellent opportunity to assess the comparative effectiveness and side effects of emerging vaccines against SARS-CoV-2. The trial platform will also allow for rapid evaluation by an experimental study design of other future interventions.

4. STUDY OBJECTIVES

4.1 Overall Objective

The overall objective is to use existing prospectively and routinely collected data from two established national cohorts (i.e. SHCS and STCS), to build a flexible trial platform and to test this platform in the frame of a randomised comparative effectiveness pilot trial of licensed vaccines against SARS-CoV-2 in regard to immunogenicity, and efficacy to prevent infections and related Covid-19 complications in immunocompromised patients. The main goals refer to 1) investigating the feasibility for setting up such a nested trial platform which makes use of routinely collected highly quality cohort data for patient identification, recruitment and outcome assessment and to 2) conducting a pilot trial of licensed vaccines against Sars-CoV-2. Such an infrastructure may allow for the accelerated set-up of randomized controlled clinical trials which are crucial for the rapid evaluation of new interventions in the situation of a pandemic.

4.2 Objectives related to platform trial set-up and feasibility of cohort based patient recruitment, trial inclusion and data collection

The study seeks to determine the feasibility for the set-up of a trial platform which is nested into the existing cohort infrastructures. This setting should guarantee a more efficient identification and recruitment of eligible immune compromised patients for intervention trials. For this we will assess a number of process parameters that relate to feasibility and recruitment of eligible patients within the pilot trial. The parameters of interest are

- Duration of RCT set up (i.e. time from deciding which interventions will be tested, achieving ethical approval until the first patient is randomized).
- Time of patient recruitment (i.e. from activation of first study site until (i) 40 and (ii) 380 patients are randomized)
- Patient consent rate (i.e. proportion of patients giving informed consent out of approached eligible patients)
- Proportion of missing data for all baseline variables from routinely collected cohort data (baseline variables are listed under “Measurements and procedures”) compromising future co-factor adjust in trial efficacy evaluations
- Proportion of missing data for all clinical outcomes from routinely collected cohort data and outcome data that is collected in the trial platform (clinical outcomes are listed below)

4.3 Objectives related to a platform based nested pilot trial to investigate the comparative effectiveness of vaccines against Sars-CoV-2

The study seeks to determine the following SARS-CoV-2 related objectives (for detailed definitions see under 5 study endpoints) which are all developed according to FDA recommendations for phase III Covid-19 vaccine licensing trials (20)):

- Immune response (pan-Ig antibodies against the receptor binding domain (RBD) in the S1 subunit of the spike protein (pan-Ig anti–S1-RBD) of SARS-CoV-2.
- newly PCR-confirmed asymptomatic SARS-CoV-2 infection,
- newly PCR-confirmed symptomatic SARS-CoV-2 infection
- severe COVID-19 infection,
- COVID-19 burden of diseases (BOD)
- Patient reported asymptomatic or symptomatic infections of household members.
- Safety parameters
    - Adverse events from vaccines and
    - Serious adverse events

4.4 Safety Objectives

To evaluate the safety of vaccines in immunocompromised patients and risks for adverse events (AEs) and serious adverse events (SAEs).

5. STUDY OUTCOMES

Due to the exploratory nature of the pilot study, no specific primary objective is defined. We distinguish three type of endpoints: immunological endpoints, clinical vaccine related effectiveness endpoints and vaccine related safety endpoints.

5.1 Immunological Outcomes

The best predictor of antibody mediated protection is assessed with neutralisation assays, in which the ability of patient serum to prevent virus infection in *in-vitro* assays is measured. These assays, however, are too labour intense for the purpose of this trial. The binding antibody response against the S1 (RBD) of spike protein of SARS-CoV-2 as assessed serological tests show a high correlation with neutralisation titers (21, 22).

Therefore, we will use a commercial immunoassay Elecsys® Anti-SARS-CoV-2 S for the in vitro quantitative determination of antibodies to the SARS-CoV-2 spike (S) protein receptor binding domain (RBD) in human serum and plasma (23). This assay detects pan-Ig antibody response (pan-Ig anti–S1-RBD) and allows for a quantitative assessment of the serological response of the participants at baseline and three months after vaccination. Additionally, we will qualitatively measure anti-Nucleocapsid (N) responses with Elecsys® Anti-SARS-CoV-2 N assay to gain a broader insight on the immune response of the participants.

Finally, we will assess SARS-CoV-2-binding antibody responses of the participants by analyzing the IgM, IgA and IgG responses to a wider range of SARS-CoV-2 proteins (S1, S2, RBD and N using an in-house method (ABCORA 2.0) established at the Institute of Medical Virology (IMV), UZH). The ABCORA 2.0 test has an advantage over commercial available tests, as it allows a parallel assessment of IgG, IgM and IgA reactivity to multiple antigens enabling a high-dimensional temporal resolution of antibody responses and a dissection between humoral responses to an infection and vaccination.

5.2 Clinical Outcomes

The clinical effectiveness endpoints are (according to FDA recommendations for phase III Covid-19 vaccine licensing trials (20)) of the following:

- Newly PCR-confirmed asymptomatic COVID-19 infection (identified by the presence of anti–SARS-CoV-2 nucleocapsid antibodies or Sars-Cov-2 PCR or rapid antigen test) and no related symptoms [(i.e. fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose nausea or vomiting, and diarrhea]) at any time point in within 48 weeks following randomisation.
- Newly PCR-confirmed symptomatic COVID-19 infection with at least one of the following symptoms (i.e. fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose nausea or vomiting, and diarrhea at any time point in within 48 weeks following randomisation
- Severe COVID-19 infection with respiratory failure, evidence of shock (as diagnosed by a treating physician), clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death at any time point in within 48 weeks following randomisation.
- COVID-19 burden of diseases (BOD), a composite of the above endpoints. The BOD is will be scored as by using 0 for no COVID-19, 1 for non-severe COVID-19, and 2 for severe COVID-19.

An additional clinical effectiveness endpoint is patient reported asymptomatic or symptomatic infections of household members.

All clinical outcomes will be measured in the trial database during a follow-up period of 48 weeks after randomisation and vaccination.

5.3 Other Outcomes of Interest

None.

5.4 Safety Outcomes

5.4.1 Collection of solicited local and systemic adverse events will for feasibility reasons be reduced to:

- any local symptom (redness or swelling or prolonged pain at injection side) limiting continuation of normal daily activities during the first 7 days after vaccination
- any systemic symptom (fever, generalized muscle or joint pain) limiting continuation of normal daily activities during the first 7 days after vaccination
- any vaccine related symptom leading to contacting a physician during the first 7 days after vaccination

6. STUDY DESIGN

6.1 General study design and justification of design

This is a pilot trial which is based on a trial platform that is integrated into the ongoing routine prospective data collection of two national cohorts, the SHCS and STCS. Eligibility of trial participants will be checked from routinely collected cohort data. Baseline data collection is done within cohorts. Randomisation and follow-up data collection of clinical trial endpoint data is done within the trial platform which is linked to the cohort database. The trial platform is overseen and managed by the two data centres of the SHCS and STCS.

A parallel two-arm open-label randomized controlled exploratory pilot trial comparing the first approved SARS-CoV-2 vaccines is planned to compare the immunogenicity, clinical effectiveness and safety of the first two licensed vaccines against Sars-CoV-2. The details of the intervention and control group will be described in a sub-protocol following the licensing of vaccines. Enrolment of patients is explained in figure 1. Cohort data centres will identify eligible patients based on routinely collected cohort data and eligible patients will be contacted for consent for participation prior to randomisation. Randomisation will be performed through minimisation with respect to cohort (SHCS, STCS), center, age (<65, ≥65 years old), sex, immune-suppression (<200 CD4 cells/µl in SHCS and uninterrupted prednisone treatment of at least 6 months in addition to standard immunosuppression.in STCS) and a random element that reduces randomisation predictability. The trial platform allows to expand the pilot trial and to add further sub-study protocols to evaluate for example vaccine strategies in patients with a first vaccination but insufficient or lacking immune response (Figure 1).

The COVID-19 pandemic has revealed a need for research infrastructure such as trial platforms, which allow for fast and efficient evaluation of multiple preventive and therapeutic interventions in case of infectious disease outbreaks. Ideally, trial platforms make use of already existing data infrastructures such as cohorts or registries. Once implemented, the present protocol is meant to provide orientation and guidance for other trial platforms.

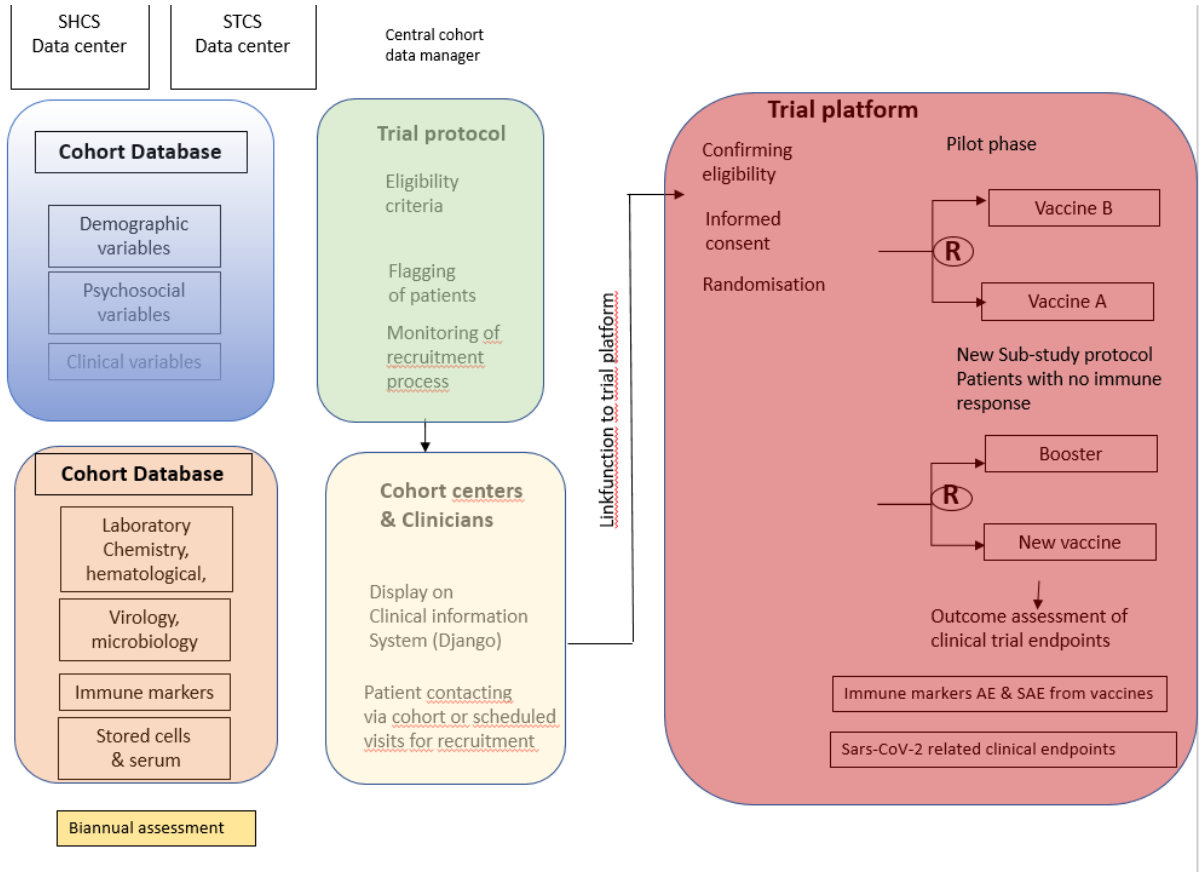

Figure 1 Trial platform for immune compromised patients from the SHCS and STCS

6.2 Methods of minimising bias

6.2.1 Randomisation

Randomisation will be performed through minimisation with respect to centre, age (<65, ≥65 years old), sex, immune suppression and a random element. This will ensure that we control for imbalance in each treatment arm while reducing the predictability of the randomisation. The randomisation will be centrally implemented into the current electronic system which all cohort centres are using. In short, the "treatment preference" is written in Python and embedded in the Django framework (plus external Python script for STCS). With R, the random allocation scheme is generated. Depending on the preference, the treatment is then assign with the help of the allocation table. Randomisation will be conducted separately for each cohort.

6.2.2 Blinding procedures

As we plan to embed the pilot trial as good as possible into the clinical routine and into the management of patient in clinical routine and within the cohort study infrastructure, we do not plan to blind treating physicians or patients. Further, also outcome assessors will not be actively blinded. Large part of the outcomes will be collected through routinely collected data (see "5. Study outcomes"). Analysis of immunological parameters will be blinded in regard to treatment groups. All the critical clinical endpoints of severe COVID-19, deaths and serious adverse events will be adjudicated by an infectiologist blinded to vaccine allocation.

6.2.3 Other methods of minimising bias

Reasons for drop outs or loss to follow-up will be assessed and investigated with the routinely established processes endorsed by each cohort to minimize attrition bias. Loss to follow-up in both cohorts is small. In the SHCS in 2019 0.5 of patients died and 2.6 dropped out and in the STCS from

2008 to 2019 only 76 of 5672 patients were lost to follow-up (1.3%).

6.3 Unblinding Procedures (Code break)

Not applicable as the study has an open design.

7. STUDY POPULATION

This is a multi-centre study recruiting patients from 4 of the 7 study centres of the SHCS and 2 of the the 6 study centres of the STCS.:

SHCS study centres:

- Department of Infectious Diseases, Bern University Hospital, University of Bern
- Division of Infectious Diseases & Hospital Epidemiology, University Hospital Basel
- Division of Infectious Diseases, University Hospital Lausanne, University of Lausanne
- Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich

STCS study centres:

- Klinik für Pneumologie, and Klinik für Nephrologie, Universitätsspital Zürich
- CHUV Lausanne, Service des maladies infectieuses, Clinique pour pneumologie et nephrologie
- Universitätsspital Basel, Pneumologie
- Universitätsspital Basel, Transplantationsimmunologie & Nephrologie,

The cohorts are explained in more detail elsewhere (14, 15, 24, 25). The study will be explained to eligible patients during their visit at the cohort centre. These visits will not be scheduled specifically for the purpose of this study.

7.1 Eligibility criteria

Inclusion criteria:

- All patients registered with informed consent from participating cohorts aged ≥18 years
- Additional consent for participation in the specific sub-protocol

Exclusion criteria:

- Acute symptomatic SARS-CoV-2 infection, influenza or other acute respiratory tract infection
- Known allergy or contra-indications for vaccines or any vaccine components
- Any emergency condition requiring immediate hospitalization for any condition
- Patients with previous PCR documented SARS-CoV-2 infection and, or documented antibodies in the last 3 months prior to screening visit (day 0).

Inclusion and exclusion criteria will be specified further when eligible interventions are identified (i.e. in a separate sub-protocol).

7.2 Recruitment and screening

Specific eligibility criteria can be defined and implemented by the trial platform data base which is based on all clinical and laboratory cohort data and managed by the cohort data centres (figure 2 and separately submitted electronic Case Report Form). Both cohorts have developed a clinical information system that summarizes all relevant clinical and laboratory information for patients and widely serves as a clinical management and decision support system. This system allows to flag all eligible patients by centre and centre physician and to make this information for the pilot trial available in the clinical information and data entry system. Thus, trial eligibility information will appear on the online cohort data entry form which is used by all participating cohort centres and physicians for data entry during cohort visits. When an eligible patient is coming to a planned cohort visit or in between consultation the treating physician will recognize the patient as eligible when open the patient specific data entry form and initiate the recruitment process. In case of logistic needs, patients may also be actively contacted and invited to come to the study centre for vaccination independent of the trial and will then be additionally informed about the purpose of this trial. This is line with the priority list established by the BAG for vaccination of high risk patients for Covid-19 infection (Details are defined in the first sub-study protocol). The eligibility checks, consent process and randomisation will be embedded into existing regular cohort or scheduled in between visits and done in a separated GCP conform clinical trials data collection system that is linked to both cohorts. The treating physician will explain the currently ongoing study to eligible patients and inform them about potential risks and benefits. According to the patients' preferences, the randomisation can be done during the same visit or at a later appointment.

7.3 Assignment to study groups

For randomisation treating physicians will use a link function in the clinical information and data entry form and be linked to the web-based platform trial data entry and randomisation page. After rechecking all inclusion and exclusion criteria and after having the trial participation consent formed singed patients will be assigned to study groups using minimisation with a random element across a number of stratification factors to control for imbalance in each treatment arm (stratification factors are cohort (STCS, SHCS), centre, age group, sex and presence of comorbidities).

Patients not consenting to participate will be vaccinated according to clinicians' judgement and be followed within the cohorts.

The trial platform will allow for adaptive randomisation for future trials.

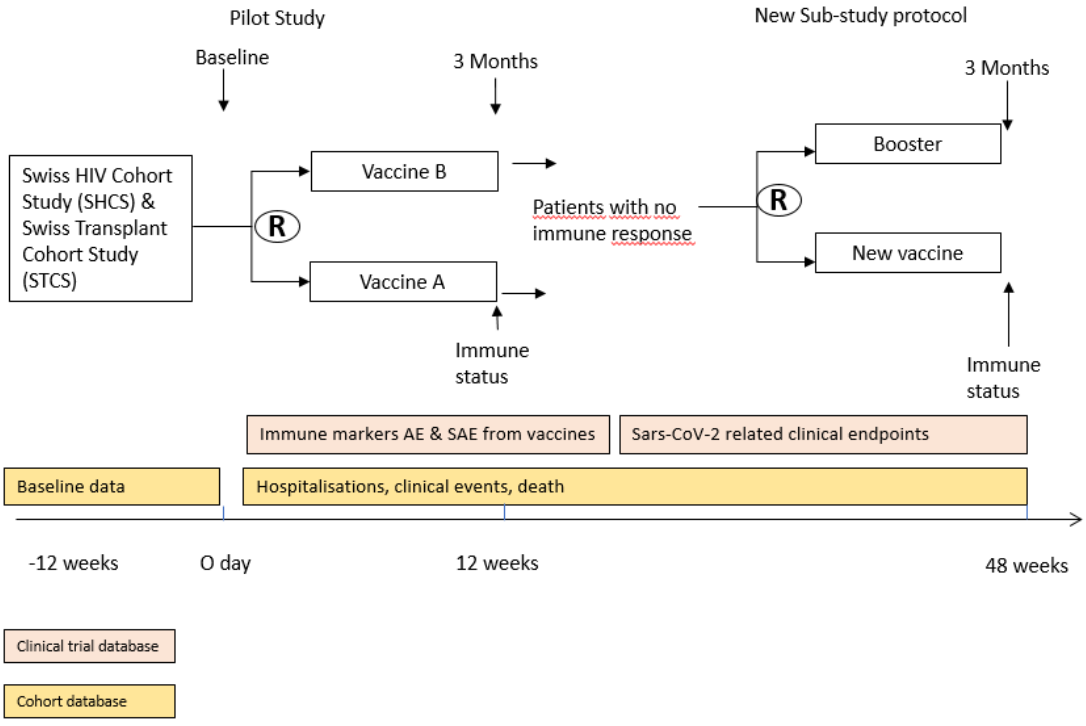

Figure 2: Randomisation of cohort participants with informed consent for trial participation

7.4 Criteria for withdrawal / discontinuation of participants

Enrolled patients have always the opportunity to withdraw from the trial without mentioning any specific reason at any time. In addition, patients can also state that they do not wish to be contacted for the study anymore and that also their physician shall not be contacted for outcome assessment. As the vaccines which will be assessed in this study (will be described in more detail in separate sub-protocol) will most likely be applied as a two-time injection, patients may withdraw from receiving a second vaccine shot. Eventual revaccination in patients with no immune response or loss of immune response will be handled by an additional sub-study protocol for these patient populations or will be conducted by individual clinicians' decision according to best clinical management outside of a study protocol. In case a second sub-study protocol will be developed for patients with no or insufficient immune response at 12 weeks follow-up, patients entering the second sub-study protocol will be censored within the firstsub-study pilot trial.

8. STUDY INTERVENTION

(SPIRIT #11)

8.1 Identity of Investigational Products (treatment / medical device)

8.1.1 Experimental Intervention (treatment / medical device)

The first SARS-CoV-2 vaccine receiving market authorisation is Switzerland. The specific intervention will be described in a separate sub-protocol as soon as the intervention is available.

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

The second SARS-CoV-2 vaccine receiving market authorisation is Switzerland. The specific intervention will be described in a separate sub-protocol as soon as the intervention is available.

8.1.3 Packaging, Labelling and Supply (re-supply)

We plan to receive vaccines through hospital pharmacies or directly through available capacities from study centres. Original packaging and labelling (i.e. no re-packaging or re-labelling required) will be used. The usual vaccine bar code tags and batch number will be stored according to local clinical practice or patient vaccination cards as made available by local clinics or vaccine producers. Vaccine batch numbers will be entered into the trial platform database.

8.1.4 Storage Conditions

Vaccines will be stored at necessary temperatures at cohort clinical centres according to recommendations provided by vaccine producers.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

The one-time (or two time, if required) injection will be applied by the treating physician or designated clinic or study nurses from the participating study centres. The specific intervention will be described in a separate sub-protocol as soon as the intervention is available.

8.2.2 Control Intervention

The one-time (or two time, if required) injection will be applied by the treating physician or designated clinic or study nurses from the participating study centres. The specific intervention will be described in a separate sub-protocol as soon as the intervention is available.

8.3 Dose / Device modifications

The vaccines which will be assessed in this study (will be described in more detail in separate sub-protocol) will most likely be applied as a one-time injection. A modification of treatment is therefore not possible

8.4 Compliance with study intervention

The application of the one-time injection by the treating physician (or a delegated person) will be documented in the trial platform data entry form.

8.5 Data Collection and Follow-up for withdrawn participants

Patients have the right to withdraw the planned follow-up visits. Clinical outcomes for those patients will be assessed from routinely collected cohort data.

8.6 Trial specific preventive measures

Trial specific permitted treatment as in usual care are based on the clinical judgment of the physician. If there are specific non permitted interventions (as indicated by the Swissmedic leaflet of the approved vaccine), this will be indicated in the separate sub-protocol.

8.7 Concomitant Interventions (treatments)

Concomitant interventions are allowed whenever necessary as in usual care based on the clinical judgement of the physician. If there are specific concomitant interventions that are not allowed (as indicated by the Swissmedic leaflet of the approved vaccine), this will be indicated in the separate sub-protocol.

8.8 Study Drug / Medical Device Accountability

Vaccines will be delivered by the hospital pharmacies of participating cohort centres.

8.9 Return or Destruction of Study Drug / Medical Device

Since the vaccines will be a product which has received marked authorisation in Switzerland, unused products could be potentially used for other patients based on the clinical judgement of physicians.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

Eligible cohort patients will be informed about the study during their next visit (not study related) at one of the cohort centres. Patients willing to participate can decide to consent and be randomised during the same visit or at a separately planned visit (see study schedule). Planned study visits are at 12 and 48 weeks after randomisation. Next to that, patients will be followed-up in the frame of the SHCS and the STCS.

Data collection and patient assessment is based on trial platform which is nested into the routinely data collection of the two cohorts. All relevant baseline data will be gathered within the cohort infrastructure.

All trial relevant endpoints will be collected within the trial platform infrastructure. Several endpoints like hospitalisations and death will continue to be collected in the cohort database as the assessment of theses outcomes is required by the cohort study protocols.

The following trial baseline data will be used from the routinely collected cohort base database:

SHCS:

Age, sex, education, working status, co-morbities (diabetes mellitus, hypertension, dyslipidemia, coronary heart diseases and strokes, body mass index), depression, smoking, alcohol and illicit drug use, current antiretroviral therapy and any co-medication, first HIV antibody test or inclusion into cohort, CD4 cell nadir, latest CD4 cell count & HI viral load, glomerular filtration rate, SARS-CoV-2 PCR and antibodies (IgM & IgG), hepatitis C virus (HCV) and chronic hepatitis B virus (HBV) infection, contact with a person with a documented SARS-CoV-2 infection, documented SARS-CoV_2 infection, date of diagnosis, hospitalization due to SARS-CoV-2 infection.

STCS:

Routinely collected relevant baseline data from the STCS include age, sex, ethnicity, history of transplantation, organ-specific pre-transplant history, length of hospital stay due to actual transplantation, patient medical history (cardiopulmonary diseases, metabolic diseases, endocrine diseases, kidney diseases, history of cancer and other events and diseases), history of major infectious diseases, immunosuppressive treatment history, patient- and organ-specific lab assessment data, transplant immunologic assessments, pre-TX serologies (HBV, HCV, CMV, HIV, EBV, Toxo, Tpha, HSV, VZV), HLA tissue-typing, allograft biopsy (date and ID), drug prescription data (induction, mantenance immunosuppression, infectious diseases prophylaxis, other drugs), occurrence of any post-transplant infectious disease including SARS-Cov-2, STCS: education, profession, working capacity, medication adherence, smoking history, drug addiction).

9.2 Assessments of outcomes

9.2.1 Assessment of feasibility outcomes

- **Duration of RCT set up (i.e. time from deciding which interventions will be tested until the first patient is randomized).**

The date when the scientific committee/trial investigators decide which intervention will be tested will be documented. The date when the first patient is randomized will be capture in the centralised randomisation system.

- **Time of patient recruitment (i.e. from activation of first study site until 40 patients are randomized)**

The date when the first study centre starts enrolling patients will be documented. The date when the first 40 patients and the last patient (number 380) are randomised will be captured in the centralised randomisation system.

- **Patient consent rate (i.e. proportion of patients giving informed consent out of approached eligible patients).**

Investigators will capture in the electronic system from the separate cohorts if a potential eligible patient was informed about the study and if the patient was actually included (i.e. randomised).

- **Proportion of missing data for all baseline variables from routinely collected cohort data (baseline variables are listed under "Measurements and procedures")**

For all baseline variables defined under 9.1 we will assess the proportion of missing data.

- **Proportion of missing data for all clinical outcomes from routinely collected cohort data and outcome data that is collected in the trial platform (clinical outcomes are listed below)**

  For all defined clinical outcomes we will assess the proportion of missing data.

9.2.2 Assessment of immunological endpoints

We will assess pan-IgG anti S (RBD) (quantitative) and anti- N antibodies (qualitative) with the commercial Elecsys® Anti-SARS-CoV-2 S and N tests at baseline and at 12 weeks following randomisation and vaccination. Patients will be invited to see their treating physician 12 weeks after randomisation (see Study schedule). During baseline and follow-up visits this visit a blood sample will be taken (EDTA blood (2 x 7.5 ml)) and assessed for the above listed antibodies:

- 1ml for Elecsys® Anti-SARS-CoV-2 N and S tests (performed locally at each laboratory)
- 2ml EDTA Plasma for ABCORA 2.0 test (performed at IMV, UZH)

EDTA blood should be processed within 24h and EDTA plasma should be stored at -20°C. For ABCORA 2.0 antibody measurements plasma samples will be collected at each center and a collective shipment will be sent after baseline and at 12 weeks after randomization and vaccination to the IMV, UZH. One sample will be stored according to SHCS and STCS protocols for later eventual analyses at the centers of University Hospital Zurich.

9.2.3 Assessment of clinical endpoints

Patients are informed to contact center physicians in case an asymptomatic or symptomatic SARS-Cov-2 infections was diagnosed outside the settings of participating cohort centers. Clinical endpoints will be assessed at 12 and 48 weeks, and during each cohort visits, that fall in between the trial specific visit dates.

- Newly PCR-confirmed asymptomatic Covid-19 infection (identified by the presence of anti–SARS-CoV-2 nucleocapsid antibodies ,or PCR or rapid antigen test) and no related symptoms [(i.e. fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose nausea or vomiting, and diarrhea]) at any time during the 48 weeks of follow-up

During all visits at the trial centres (study specific at 12 and 48 weeks, as well as cohort visits) a PCR SARS-COV-2 test will only be conducted if the treating physician would also conduct such a test during clinical routine (e.g. exposure to infected individual). PCR tests done in between independently will be recorded with dates and results. In case of a positive test result, physicians will check for symptoms and patients will be followed-up according to clinical routine and physicians' judgement.

- Newly PCR-confirmed symptomatic Covid-19 infection with at least one of the following symptoms (i.e. fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose nausea or vomiting, and diarrhea) at any time during the 48 weeks of follow-up

During all visits at the trial centres (study specific at 12 and 48 weeks, as well as cohort visits) a PCR SARS-COV-2 test will only be conducted if the treating physician would also conduct such a test during

clinical routine (e.g. COVID-19 related symptoms; exposure to infected individual). In case of a positive test result, physicians will check for symptoms and patients will be followed-up according to clinical routine and physicians' judgement.

- Severe COVID-19 infection with respiratory failure, evidence of shock (as diagnosed by a treating physician), clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death at any time during the 48 weeks of follow-up.

- Covid-19 burden of diseases (BOD), a composite of the above endpoints. The BID is will be scored as by using 0 for no COVID-19, 1 for non-severe COVID-19, and 2 for severe COVID-19.

The burden of diseases endpoint will be assessed by combining the before listed outcomes (i.e. no COVID-infection, non-severe COVID-19 infection

- Patient reported asymptomatic or symptomatic infections of household members.

Patients will be asked at the 12-week and 48-week visit if a household member was diagnosed with COVID-19.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events following vaccination

Any local symptom (redness or swelling or prolonged pain at injection side) continuation of normal daily activities during the first 7 days after vaccination
During the 12-week visit, patients will be asked if they had any local symptoms which limited their daily activities during the first 7 days after vaccination.

- Any systemic symptom (fever, generalized muscle or joint pain) limiting continuation of normal daily activities during the first 7 days after vaccination.

  During the 12-week visit, patients will be asked if they had any systemic symptoms after randomisation which limited their daily activities during the first 7 days after vaccination.

- Any vaccine related symptom leading to contacting a physician during the first 7 days after vaccination

  During the 12-week visit, patients will be asked if they had to contact a physician within 7 days after vaccination.

9.2.4.2 Serious adverse events

For reporting of serious adverse events we will adhere to the ICH E2A guidelines (26) and define a serious adverse event (experience) or reaction 'as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Exemptions will be SARS-CoV-2 related deaths or SARS-CoV-2 related hospitalisations, which are among the assessed clinical outcomes. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe'.

9.2.4.3 Laboratory parameters

Specify laboratory parameters to be assessed; define when abnormal laboratory parameters will be

considered as adverse events, define time-points of assessment; describe sampling if deviating from hospital routine; specify tests to be used (e.g., for pregnancy: blood, urine; urinalysis); describe analysis of samples: local or abroad, if abroad, describe procedure for shipment, storage until shipment; if not yet known, refer to instruction to be written for the study team and to be part of the study manual.

Laboratory parameters besides immune response parameters will be assessed at bi-annually cohort visits according to the cohort protocols.

9.2.4.4 Vital signs

Not relevant for purpose of this trial.

9.2.5 Assessments in participants who prematurely stop the study

All clinical outcomes will be assessed from routinely collected cohort data which will also be available if patients decide to prematurely stop participating in the clinical trial.

9.3 Procedures at each visit

9.3.1 Eligibility (and eventual enrolment randomisation)

Visit 1; Day -90 – 0: All patients from the two cohorts (i.e. SHCS and STCS) will prospectively be assessed for eligibility based on the cohort study based trial platform. Eligible patients will be either contacted ahead by cohort centres and informed about the trial and availability of vaccines or directly informed during in between visits or cohort study visits. Based on the patients preferences they will have the option to start participating in the study (i.e. sign consent form, being randomised and eventually receiving the intervention or control) during the same visit or at a separate agreed on visit (see also “Study schedule”). Patients requiring vaccination without trial participation will be vaccinated.

9.3.2 Enrolment and randomisation

Visit 2; Day 0: Patient will return the signed consent form which will also be signed by the treating physician. The patient will then be randomised by the treating physician and receive the intervention or control (applied by treating physician or delegated personnel). For patients who were already enrolled and randomised during visit 1, visit 2 will be skipped (see also “Study schedule”). For women in childbearing age it is required to make sure that they are not pregnant (i.e. conduct a pregnancy test) before they get vaccinated and a contraception is required for 12 weeks after the first vaccination dose.

9.3.3 Follow-up 1 week 12

Patients will be asked with 3 questions in regard to side effects from vaccination during the first week following vaccination. Occurrence of asymptomatic or symptomatic COVID-19 infection, serious COVID-19 infection and hospitalisation for any reason will be investigated, the dates of events will be requested and entered into the trial data collection form. All routine data and blood samples following protocols of the SHCS and STCS will be collected as usual and entered into the respective cohort database.

A blood sample will be taken for investigating post- vaccination immune status at week 12 in all patients.

9.3.4 Follow-up 2 week 48

Occurrence of asymptomatic or symptomatic COVID-19 infection, serious COVID-19 infection and hospitalisation for any reason will be investigated, the dates of events will be requested and entered into the trial data collection form. All routine data and blood samples following protocols of the SHCS and STCS will be collected as usual and electronically forwarded into the respective cohort databases.

A blood sample will be taken for investigating post- vaccination immune status.

10. SAFETY

10.1 Drug studies

We follow the definition of the ICH E2A guidelines (26). An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Note that other categories can be used. However, a definition has to be provided in the protocol.

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR. The information if the SAE is a potential SUSAR is a mandatory

field in our electronic case report form for SAEs (see separately submitted electronic case report form).

Assessment of Severity

The “Common Terminology Criteria for Adverse Events CTCAE Version 6.0” (27) terminology is going to be used to assess the severity of adverse events (i.e. 1 – Mild, 2 – Moderate, 3 – Severe, 4 – Life-threatening, 5 – Death).

10.1.1 Reporting of serious adverse events (SAE) and other safety related events

All SAEs must be reported within 7 days to the Sponsor-Investigator of the study. The Sponsor-Investigator will be averted in case a local investigator is reporting a SAE in the trial electronic data system by the cohort data centers. The Sponsor-Investigator will confirm or adapt the SAE and return the form to the site.

SAEs resulting in death are reported to the Ethics Committee via BASEC within 7 days.

The other in the trial involved Ethics Committees receive SAEs resulting in death in Switzerland via Sponsor-Investigator via BASEC within 7 days.

Exemptions will be SARS-CoV-2 related deaths which are one of the assessed clinical outcomes.

Reporting of SUSARs

SUSARs will be reported to the Ethics Committee via BASEC within 7 days if the event is fatal, or within 15 days (all other events). The Sponsor-Investigator must inform all Investigators participating in the clinical study of the occurrence of a SUSAR. All in the trial involved Ethics Committees will be informed about SUSARs in Switzerland via BASEC according to the same timelines. .

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the Ethics Committee (local event via local Investigator) via BASEC.

Closure of a sub-study protocol due to a negative benefit-risk ratio is reported to the Ethics Committee within 7 days.

The Sponsor-Investigator must immediately inform all participating Investigators about all safety signals. The other in the trial involved Ethics Committees will be informed about safety signals in Switzerland via the Sponsor-Investigator.

Reporting and Handling of Pregnancies

Participation of pregnant women will be decided when vaccine related safety reports and recommendations are published by the producers. At present natural history data indicate no increased adverse pregnancy outcome of women with Sars-CoV-2 infection (28):

Periodic reporting of safety

No annual safety report will be submitted as this will be a Category A study.

10.1.2 Follow up of (Serious) Adverse Events

During the study every step is taken to ensure, that all (S)AEs are identified and documented. Treating doctors and study centres are responsible to treat the (S)AEs and follow-up (S)AEs. At the last follow-up at week 48 it is ensured, that all (S)AEs are identified and well treated. If a (S)AE occurs, all efforts will be undertaken to treat these (S)AEs (i.e. antiallergic treatment in case of an allergic reaction) and follow-up until it is resolved is ensured. If patients are lost to follow-up at the last follow-up visit, at least 3 attempts to contact them (by call and letter) should be made to contact them and assess why they were lost to follow-up.

10.2 Medical Device Category C studies

Not applicable.

10.3 Medical Device Category A studies

Not applicable.

10.4 Assessment, notification and reporting on the use of radiation sources

Not applicable.

11. STATISTICAL METHODS

11.1 Hypothesis

The goals are 1) to assess the functionality of our trial platform that is nested in established national cohort (i.e. STCS and SHCS) and 2) to run a comparative effectiveness pilot trial of the first two licensed vaccines against SARS-CoV-2 infection with the aim to compare immunogeneity, safety and clinical efficacy of these vaccines in immunocompromised patients. We aim to power our trial to test for non-inferiority of the immune response of the second licensed vaccine compared to the first licensed vaccine in randomised individuals from both cohorts. Formal hypothesis testing will be formulated in a separate sub-protocol.

11.2 Determination of Sample Size

This study is planned as a pilot study and aims to enrol patients for a period of 3 months. Sample size calculation will be provided in a separate sub-protocol, once relevant sub-group results of the phase III licensing vaccine trials pertinent to patients of this trial are published. We aim to power the pilot trial for non-inferiority of the immune response of the second licensed vaccine compared to the first licensed vaccine

11.3 Statistical criteria of termination of trial

For future sub-study protocols that may involve adding or dropping of study arms based on results from interim analyses a detailed action plan, an analysis plan with stopping rules for harm, benefit and futility will be established.

No interim analysis is planned during the pilot trial and termination will not be based on any statistical criteria.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

Patients will be analysed according to their allocated randomisation group (intention to treat [ITT]). The pilot trial will inform us on the amount of missing variables. We will not have missing baseline information that define eligibility criteria or that are considered for the randomisation. The amount of missing values for the clinical outcomes will be assessed (see section 11.5. Handling of missing data and drop outs for more details).

11.4.2 Feasibility analysis

Actual time spans will be reported (i.e. how long it took to (i) set up the trial; and (ii) enrol patients (accrual time)). Proportion and number of consenting patients and missing data will be reported.

11.4.3 Analyses of immunological and clinical outcomes

Immunological outcomes at 12-week follow-up will be reported as frequency and percentage of positive serologic immune response for both vaccine arms and we will test for non-inferiority of the second licensed vaccine *versus* the first licensed vaccine.

Clinical outcomes and patient-reported outcomes of household members will be described for both treatment arms. Detailed analysis will be provided in a separate sub-protocol.

11.4.4 Interim analyses

No interim analyses will be done.

11.4.5 Safety analysis

Safety endpoints will be reported for each study arm using summary statistics (frequencies and percentages). We expect safety issue to be small and do not believe that we will have enough power to demonstrate any statistical difference between the treatment arms.

11.4.6 Deviation(s) from the original statistical plan

If there are any deviations from the pre-specified analysis planned, these will be clearly indicated and justified in the publication of the primary results.

11.5 Handling of missing data and drop-outs

We will report the number of drop-outs and reasons for drop-outs for each treatment arm separately. Reasons for drop-outs will be carefully explored for a deeper understanding of the drop-outs. In this pilot study, patients with missing outcomes will be dropped from the clinical outcome assessments. Patient characteristics of the dropped population will be compared to patient characteristics of the trial participants that have an outcome to avoid further bias.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

Data will be recorded with electronic Case Report Forms (eCRF) provided by the REDCap Software. For each enrolled study participant, a eCRF is maintained. A unique patient identifier will be used to identify patients (i.e., the same identifiers used in the respective cohorts, Swiss HIV Cohort Study (SHCS) and Swiss Transplant Cohort Study (STCS)).

All participating physicians will be authorized to enter data in the eCRF.

12.1.2 Specification of source documents

Source data will include all study documents, like e.g. informed consent forms, online AE/SAE forms etc. Source data will be available at all sites and may be found in paper or electronic form.

All source data is available at the local cohort centers via the routine cohort data collection and online display forms.

Source data are the routinely collected and under 9.1 defined baseline data, all routinely within the cohort structure collected laboratory and the clinical endpoint and safety data and immunogeneity parameters which will be collected within the trial data collection infrastructure.

12.1.3 Record keeping / archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the trial. Data will be extracted from REDCap and stored on the server of the University of Zurich. Any study relevant paper documents will be archived at each site for a minimum of 10 years.

12.2 Data management

Study data will be captured via REDCap, based at the data centre of the Swiss HIV Cohort study. The data collected is entered into the study eCRF. Baseline data available in the two participating cohorts (SHCS and STCS) is transferred directly from the cohorts into REDCap. The REDCap platform offers an audit trail to maintain a record of initial entries and any changes made, time and date of entry, user name of the person authorizing entry or change. The principal investigator at the study site will be responsible for assuring that the data entered into the eCRF is complete, accurate, and that the entry and updates are performed in timely manner.

If a patient withdraws from the trial or is lost to follow up, the reason for drop-out will be reported on the corresponding eCRF. If the patient withdraws from the cohort, a cohort specific stop follow-up form is in place.

12.2.1 Data Management System

The eCRF will be implemented by the data centre of the SHCS at the University of Zurich using REDCap. REDCap is installed on the server of the University of Zurich and maintained by the IT department of the University of Zurich. Additional storage capacity can be added if needed. Data entry will be performed by participating clinicians.

12.2.2 Data security, access and back-up

The REDCap platform is accessible via a standard browser on devices with internet connection. Password protection ensures that only authorized study investigators, monitors and local authorities (if necessary) will have access to the data during and after the study. User administration is centrally done by the cohort data centers, and user training is performed online by the Principal investigator and local responsible investigator. REDCap offers an audit trail system maintaining a record of initial entries and changes made, time and date of entry, and user name of person authorizing entry or change.

Back-up of REDCap data is performed daily at the server of the University of Zurich. As the trial platform and sub-studies are nested into the existing data-bases of the SHCS and STCS patient IDs from the respective cohorts are taken when cohort participants are enrolled into a sub-study.

12.2.3 Analysis and archiving

The REDCap project will be locked after eCRF data entry is completed, all data has been monitored and raised queries have been resolved. The complete study data set is exported from the REDCap database and transferred to the study statistician as well as the principal investigator through a secure channel. The statistical analysis will be performed by the involved statistician at the University Hospital of Basel. The exported data will be archived for 10 years at the server of the Swiss HIV Cohort Study at the University of Zurich.

Details and analysis and archiving are listed in the appendix documents 1 and 2.

12.2.4 Electronic and central data validation

Data entered into the REDCap platform will be validated for completeness and discrepancies automatically. In addition, the data will be reviewed by the responsible investigators . A regular download of the database will be performed and checked by the study statistician for missing values and correctness. All investigators have to respond to any resulting query and confirm or correct the corresponding data. Thereafter, the query can be closed.

12.3 Monitoring

Data monitoring will be exclusively done centrally within the infrastructure and processes established by each cohort. Weekly check-up of data entries into the clinical trial platform is done by the central data manager and the trial biostatistician.

The following central data monitoring steps are planned.

Patient recruitment will be centrally controlled and compared with the total number of eligible patients per center and cohort and the number of patients enrolled.

Selection bias: Baseline characteristics of patients included into the trial and those vaccinated outside the trial can be compared to check whether the trial population is representative in respect to the cohort population.

Trial inclusion: The responsible biostatistician/data manager will regularly check whether no patients violating an inclusion / exclusion criteria is recruited into the trial.

Population description: The responsible biostatistician/data manager will check whether according to the baseline cohort data used for the pilot trial is complete and no data is missing (see also feasibility endpoints).

Intervention: For each patient included into the trial local data managers and the central data managers will check whether patients received the same first and booster vaccines within a 3 weeks period. Co-medication will be recorded within the cohort data base infrastructure.

Primary endpoint: Site responsible investigators will regularly check that all samples are taken and stored at the site laboratories and shipped to the central laboratory. The trial data manager / biostatistician will control that all samples results are adequately entered into the trial platform data base.

Secondary endpoints: Local and central cohort data managers will regularly check that all secondary endpoints are completely entered into the trial platform and into cohort data base.

On-site monitoring visits are possible according to GCP 5.0.4, in case larger quality breaches are identified during the central data monitoring.

12.4 Audits and Inspections

The study documentation and the source data/documents are accessible to auditors/inspectors and

questions are answered during inspections. All involved parties must keep the patient data strictly confidential.

Both cohorts have an annual local inspection at each center in place with random charts checks for consistency of all data entries.

12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections.

Study data entered into the eCRF is only accessible by authorized persons. Once all data is entered into the REDCap platform and monitoring is completed, the database will be locked and closed for further data entry. The complete dataset is then exported and transferred to the study statistician as well as the principal investigator through a secure channel.

12.6 Storage of biological material and related health data

Samples of serum and cells are collected in the SHCS biannually and in the STCS linked to the current transplantation and harvested at baseline, and the 6-month and 12-month visit. Procedures for data sampling and storage according to the cohorts' standards are described in the appendix documents 1 and 2.

13. PUBLICATION AND DISSEMINATION POLICY

All trials that are set-up within the trial platform and results from sub-studies will be published (also negative results or if a trial has to be discontinued) open access in peer-reviewed journal publications. We intend to publish this master protocol together with the subsequent sub-protocols in a peer reviewed journal and on Open Science Framework (OSF). Authorship to publications will be granted according to the rules of the International Committee of Medical Journal Editors (ICMJE).

14. FUNDING AND SUPPORT

14.1 Funding

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14.2 Other Support

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15. INSURANCE

As the assessed intervention will be an approved SARS-CoV-2 vaccine (Category A study), no separate insurance is required.

In case this study will receive another risk categorisation, an insurance will be provided by the sponsor which will be acquired after receiving ethical approval for the master protocol and the sub-protocol (proof will be submitted to the CEC before the first patient is enrolled).

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17. APPENDICES

Appendix document 1

Data Management Plan for the routinely collected cohort data SHCS

Issues	
1 Data collection and documentation	
1.1 What observational data is collected observed and generated?	**Data collection:** SHCS questionnaires: Demographic, clinical, laboratory and risk behavior data is collected in biannual follow-up visits from all SHCS participants. All SHCS variables are listed in the publicly available code book www.shcs.ch/307-shcs-code-book. The data package is distributed in the form of csv-files, Access file and STATA dta-files. Volume: 62 tables, 800 MB SHCS bio bank: Plasma and cell samples are stored of every SHCS participant. The SHCS bio bank contains around 450'000 plasma and cell samples, and around 90'000 DNA samples. Information about the samples is distributed along with the SHCS questionnaire information. SHCS resistance data base: The SHCS drug resistance data base contains around 24'000 sequences of 12'000 patients in the format of FASTA files.
1.2 How is routinely collected cohort data collected, observed or generated? - What standards, methodologies or quality assurance processes will you use?	Standards and methodology: Data collection in the SHCS follows detailed standardized operating procedures (SOPs), see http://shcs.ch/238-handbooks. Details about every collected variable (data type, e.g. free text, choice, binary) is described in the publicly available code book, see www.shcs.ch/307-shcs-code-book Quality assurance processes: The SHCS data entry tool includes a three-step quality control. In a first step the physician/study nurse enters the data, in a second step a local data manager or research associate verifies the entries, in a third step, the entries undergo a final check at the datacenter. Integrated audit trails allow the tracking of changes at any time. Each registry includes the name of the person who collected the information and data of collection. Each time a follow-up visit has been registered, a graphical summary of the most relevant clinical data is sent to the physician. This feedback is a supplementary quality control and motivates the physician in reporting data of good quality. In addition, at least once a year, a collaborator of the data center visits each of the 7 collaborating centers. The quality of the information collected at the follow-up visits

	is checked on a random sample of documents. The collaborator of the data center extracts the data from the patient chart and compares the result with the data previously reported.
	The database of the SHCS consists of more than 70 data tables, which are ordered by topic (eg demographic data, clinical data, treatment data, event data, laboratory data). The tables are available in different formats (including CSV, Access and STATA .dta files). 15 Tables are descriptive and include metadata, which provide information on data interpretation (eg explanation of the codes used for diseases, medications, laboratory values etc.). Detailed metadata on SHCS variables is summarized in the SHCS code book, which is freely available on the open SHCS website http://www.shcs.ch/userfiles/file/code_book/SHCS_Variables_6.2.pdf. (see also Section 3.1, Data export for research, in the grant application) HIV genotypic resistance tests are performed by four authorized laboratories in Switzerland. The sequences are stored in a central database (SmartGene; Integrated Database Network System version 3.9.0). Record linkage is done and allows the SHCS to use these data for research. The SHCS has developed specifications, which allow an automated transfer of lab values between the university hospitals and the SHCS data center. This process is highly efficient and ensures a high data quality.
2.1 How are ethical issues addressed and handled?	The SHCS was approved by the local ethical committees of the participating centres: *Ethikkommission beider **Basel** ("Die Ethikkommission beider Basel hat die Dokumente zur Studie zustimmend zur Kenntnis genommen und genehmigt."); Kantonale Ethikkommission **Bern** (21/88); Comité départemental d'éthique des spécialités médicales et de médecine communautaire et de premier recours, Hôpitaux Universitaires de **Genève** (01–142); Commission cantonale d'éthique de la recherche sur l'être humain, Canton de **Vaud** (131/01); Comitato etico cantonale, Repubblica e Cantone **Ticino** (CE 813); Ethikkommission des Kantons **St. Gallen** (EKSG 12/003); Kantonale Ethikkommission **Zürich** (KEK-ZH-NR: EK-793), and written informed consent was obtained from all participants.* <u>Open data statement:</u> The individual level datasets generated or analyzed during the current study do not fulfill the requirements for open data access: 1) The SHCS informed consent states that sharing data outside the SHCS network is only permitted for specific studies on HIV infection and its complications, and to researchers who have signed an agreement detailing the use of the data and biological samples; and 2) the data is too dense and comprehensive to preserve patient privacy in persons living with HIV. According to the Swiss law, data cannot be shared if data subjects have not agreed or data is too sensitive to share. Investigators with a request for selected data should send a proposal to the respective SHCS address. The

	provision of data will be considered by the Scientific Board of the SHCS and the study team and is subject to Swiss legal and ethical regulations, and is outlined in a material and data transfer agreement.
2.2 How will data access and security be managed?	The SHCS data remain encrypted (no names or addresses are collected); they are identified by a five-digit study number. Patients personal information is accessible only to individuals who are directly involved in the treatment (physicians, consulting staff, laboratory staff). Data for research is distributed via a secure drop-file system provided by the University of Zurich, the download links are sent to researcher who signed the Data transfer agreement. Some key variables potentially allowing identification of the patients are excluded from the data export for researchers, and are only available on request for specific research projects. These variables include the date of birth (data export only includes birth year), canton of residence, nationality, specific information about the route of HIV infection, details on education, etc. The column "access" in the SHCS code book (http://www.shcs.ch/userfiles/file/code_book/SHCS_Variables_6.2.pdf) indicates whether the variable is included in the download for all researchers.
2.3 How will you handle copyright and Intellectual Property Rights issues?	Use of SHCS data is regulated by the respective SOPs. Use of data is subject to approval of the respective projects by the SHCS scientific board. The guidelines for nested research projects are available at http://www.shcs.ch/130-guidelines-for-nested-research-projects . Data sharing with collaborators is regulated and data transfer agreements need to be signed before data is transferred.
3.1 How will your data be stored and backed-up during the research?	This SHCS data is stored centrally at the SHCS datacenter at the University of Zurich with standardized back-up protocols. An automatic back up is performed every night.
3.2 What is your data preservation plan?	SHCS data are stored permanently and are available for future studies provided that the respective projects are approved.
4.1 How and where will the data be shared?	All interested researchers can access SHCS data provided that a respective proposal is approved by the SHCS scientific board. The SOPs to submit research proposals for everybody are openly available on the website since many years and have further been clarified (http://www.shcs.ch/132-who-can-submit). This solution ensures both access to data to all interested investigators as well as protection of sensitive data of all study participants.
4.2 Are there any necessary limitations to protect sensitive data?	Open access to all SHCS data is currently not possible, because this data is too dense and comprehensive to preserve patient privacy in patients with HIV-infection. Free access to all data would not be compatible with the SHCS informed consent and with preserving patient privacy. The open data statement is publicly available:

	http://shcs.ch/294-open-data-statement-shcs

Data Management Plan for the routinely collected cohort data STCS

Issues	
1 Data collection and documentation	
1.1 What observational data is collected observed and generated?	The core data structure of the STCS is the patient-case system: a framework that reflects the post-transplant patient process involving the collection of a multitude of data on patients, transplantations and allografts from transplantation until end of follow-up or death of the patient. The STCS data model reflects every transplant type and the monitoring of each whatsoever complex transplant scenario. The STCS patient-case system allows distinguishing data that accrue in relation to the patient from data related to the transplanted organ(s). We therefore define a ‘‘case’’ as any solid organ transplantation (SOT) of a given patient. A patient may have one or several cases, and one case can involve one, or simultaneously more than one allograft. Each case nested within a patient has its own time axis and follow-up. Patient-data, captures information which is of systemic nature and that relates to the patient, but not to the transplant itself. In contrast, case (transplant) data captures information restricted to the transplantation and to the allograft(s). Any SOT in Switzerland since May 2008 is captured in the STCS. Patients with any first, re- or second SOT, since May 2008, are enrolled in the STCS. A re-transplant is a repetition of the same SOT after failure of the previous transplant, e.g. a kidney re-transplanted after loss of function of the previous kidney allograft. A second or consecutive SOT refers to a subsequent SOT that differs from the previous type of allograft, e.g. a pancreas transplantation following a successful renal transplantation. The STCS’ data infrastructure consists of the following main layers: 1. Non-genetic health related personal data from transplant recipients, donor-recipient matching data and donor-derived allograft data (short “clinical data”) 2. Genomic data 3. Bio banking of biological material 4. Project-related “add-on” data 5. External “third party” or linkage data. Non-genetic health related personal data from transplant recipients The STCS data model assigns unique patient and transplant identification numbers. Linkage of patient and transplant data allows reconstructing the entire transplantation process with longitudinal time updating of both patient and transplant information, as well as

	the capture of intermediate events. On the patient-level, data collection involves, content wise: the psychosocial questionnaire (PSQ), medication-, comorbidity-, infectious disease-, cancer-, routine lab-, genetic- and causes-of-death data. Specific sections exist for medication data (including induction, maintenance immunosuppression, infectious disease prophylaxis and a selection of relevant "other" drugs). On the transplant and organ level, data collection focuses on the sampling of biological material (see 1.2.1 section Biological data (STCS Bio-banking) for further information), transplant-program specific data, organ function and survival, immunologic events, transplant-specific lab data and causes of graft failure. Moreover, biopsy samples that are taken during routine transplantation care, either at the time of transplantation (time zero biopsy) or during post-transplant follow-up, are important for the STCS and entered into the STCS database system. The STCS itself does not store biopsy material, but stores the biopsy's identification numbers, which are assigned by the pathology institute of the respective center where the biopsy is stored. This means that the biopsy material can be made available for given questions within the framework of approved nested projects (NP). All non-genetic meta-data descriptions including the type, format and content of each variable and dataset (eCRF) is available via the electronic metadata codebook (ecodebook) of the STCS (https://www.stcs.ch/data-portal/data-descriptions), in a version control manner. After transplantation, each patient remains associated with his or her transplant center, the center responsible for the care of the patient ("care center"). If two transplant centers simultaneously care for the same patient, both centers share and modify the same eCRFs. STCS plans to include in the data collection information as to whether the patient has signed the "General Consent" of the transplant center. Donor-recipient matching data and donor-derived graft data In order to initiate the transplantation process, the transplant team needs specific data from the organ donor to test the suitability of an organ offer for a given transplant candidate. This pivotal routine data is shared with the transplant center by the SOAS or by direct communication between clinics prior to organ procurement. If the transplant team of the transplant center accepts the organ offer, the transplant procedure can be released. The STCS collects a limited set of donor-recipient matching data and of (donor-related) graft data to assess the matching (e.g. HLA-typing, DSA, blood groups) and the quality of the transplanted organ (e.g. donor age, gender, ischemic time). Donor-recipient data linkage is ensured via the unique Swiss Organ Allocation System IDentification numbers (SOAS-IDs), which are centrally generated by the SOAS (FOPH) and transferred to the STCS. Genetic data Individual's genetic data are obtained from coded biological material

	(DNA) by large-scale genotyping methods (e.g. genome-wide association studies (GWAS) or new generation sequencing (NGS) technologies which measures many hundreds of thousands to millions variants (e.g. single nucleotide polymorphisms (SNP), deletions, insertions, copy number variations (CNV)) at the same time. The collection of genetic data for further genetic screening is limited to very little personal information, including sex and ethnicity. "Add-on" data and biological material We refer to as "add-on" data as routine clinical care data or routinely collected biological material from transplant centers or closely related resources (e.g. related healthcare providers) that are collected upon enrolled STCS patients in addition to existing STCS data. "Add-on" data are collected in the context of Scientific Committee approved NPs and serve to enhance the granularity of the data for a specific NP. The NP investigators are responsible to comply with the legislation and for meeting the regulatory requirements for the management of "add-on" data (see also Scientific Committee Guidelines, https://www.stcs.ch/research/information-for-researchers). Such "add-on" data is collected separately from the STCS database system and stored by the investigators. "Add-on" routine biological material produced as part of standard treatment can, similarly as "add-on" data, be further used for research in compliance with regulations in the context of specific NPs. It is important to note that each NP is subject to competent EC review and approval, (see also Scientific Committee Guidelines, https://www.stcs.ch/research/information-for-researchers). External "third party" data sources and data linkage We refer to "third party" data as data sources that are independently collected and stored from the STCS. Third party data is of interest for data quality control or for re-use for research. The STCS and the corresponding third party are responsible for the proper management of third party data i.e. storage, archiving and further use for research according to regulatory requirements. Third party data may or may not be linked to STCS data. The STCS re-uses data from third parties and shares its data with third parties as part of its data governance structure and upon EC approval. Table 1 provides examples of third-party data, data sources and the purpose of use. However, it is important to note that this summary is not exhaustive and that in the future further sources may become available for linkage and use for research.
1.2 How is routinely collected cohort data collected, observed or generated?	The STCS uses a professional electronic data capture system (EDC) with web-based collection and management of clinical data and bio-bank related data. The STCS IT system is currently hosted by SciCORE and maintained by SciCORE and SIMED and has been continuously developed over the last years in collaboration with the STCS DC and the users at the transplant centers (see section 2.2).

- What standards, methodologies or quality assurance processes will you use?	What standards, methodologies or quality assurance processes will you use? **1.2.1 Data processing** Clinical data Data can be exported from the STCS DB system at any time. Raw encoded STCS data are initially stored within the landing zone of the STCS tenant at sciCORE (section 2.2). From there, only authorized members of the STCS DC exports the data and securely transfer them to the DC via upload to the ownCloud platform, a secure file sharing service that is provided by the Clinical Trial Unit Basel. From there, the properly formatted raw data tables are stored for further processing within the STCS DC within the USB IT secure framework. Processed data marts are stored in different user-friendly file formats and distributed to end users (researchers) twice a year via a password-protected web interface (https://www.stcs.ch/data-portal/data-downloads) hosted within the STCS tenant on sciCORE. Two-factor authentication will soon be implemented to improve access control of research data (data and samples access policy). All further data steps are performed under the responsibility of the STCS DC, like the export validation and the data processing: ● Export Validation (EVAT) procedure: cross-checking of the extracted STCS data versus the STCS electronic codebook (eCB) to assess conformity with STCS data definitions (e.g. formats, ranges, missing value definitions). ● Data processing: Rearrangement of the STCS data for the purpose of data quality assessment, data quality reporting and data analysis (research and reporting). o The "Level 2" data processing refers to rearrangement of the STCS raw data for the purpose of data quality assessment and "hand" inspection of the data; o The "Entity Relationship data" (ER data) and "analysis layer" data processing refers to the processing of the data ready for statistical analysis with an additional option to produce customized data for specific research projects. **1.2.2 Data quality management** *Clinical data* Data quality checks refer to the totality of automatic software processes that perform in depth testing of the accuracy of the STCS data. Complex checks that consider several content wise related database fields, potentially across different fs are performed on database exports based and on specific data processing steps. In principle, data are tested for consistency and completeness at the DC through the Data Quality management System. The STCS Data quality management system (DQMS) is a collection of scripts and folders used to assess, report back to the centers and store

	checks performed about the completeness and consistency of a specific extraction of the STCS data. Consistencies checks are performed either on a regular base or they are implemented ad hoc, usually for a given research project running on the cohort data. The data queries often involve clinical expertise and they precisely reflect the data collection processes that go alongside transplantation. The DQMS is constantly being expanded. Any time a research project finds a discrepancy or a new issue of data consistency, we include it in the DQMS and, whenever possible and of long-term use, we generalize it. Feedback loop and query resolution: identified issues are "queried" back to the transplant centers (STCS sites) for resolution. The resolution is monitored by direct communication with the study sites and by comparing current and previous data extractions. The repetitive loops of data checks, site feedback and query resolution, expor, data check and monitoring of resolution, etc… lead to an ongoing improvement of data quality. Data checks run according to defined priorities (Q1, Q2, Q3, project specific) and agreed-upon timelines for issues resolution (see table in the appendix A). ● Q1: checks necessary for the processing of the STCS Annual Report ● Q2: generic checks relevant for most research projects that reuse the STCS data (for example query of the drug repository ("drug query"), biopsies- and rejection data ("biops- and rj-query"), or infectious disease data ("ID query")). Checks involve completeness and consistency. ● Q3: any checks that have been included thanks to findings from a research project or that are carried out on request for a specific STCS project. The DQMS consists of the following objects/structures and it is completed by the internal SOP documents: ● DQMS system directory, accessible from any member of the DC, where the scripts and files necessary to create the checks output are stored. ● A structured folder where the output sent to the centers or the draft useful to the further assessment of the resolution status are stored together with the feedback from the centers. ● The storage of additional documentation on a project management platform (Asana combined with google drives documents) where to keep track of the implemented checks and addressed issues on the last round. Outputs of the data quality system and feedback from the centers are stored by the STCS DC and used to monitor and validate the resolved issues on the next extraction of the data. Centers-specific reports are distributed to the centers. On top of the DQMS a Data Quality Reporting (DQR) tool is being gradually implemented by the DC of the STCS. It involves the

	generation of automatic data quality reports distributed to the STCS centers and the project investigators. DQR tools are currently under development but will involve the provision of regularly produced reports for the different transplant programs, for each transplant center and for STCS working groups. The focus is on consistency and data completeness. These tools are based entirely on the STCS metadata system (eCB). *Quality control by cross-checking with other registries* Follow-up of patients that return back on dialysis after renal allograft failure can be very demanding for the transplant centers. Mortality data of patients on dialysis after renal allograft failure is therefore cross-checked for data quality purposes with the Swiss Renal Registry and Quality Assessment Program (srrqap). The Federal Ordinance on Transplantation6 imposes that several post-transplant outcome parameters have to be monitored and reported to the Federal Office of Public Health (FOPH) on a yearly basis (Art. 20). This includes for example a yearly follow-up of all transplanted patients or that certain key transplant monitoring data recorded by the Swiss Organ Allocation System (SOAS) have to be cross-checked with the data from the transplant centers (i.e. the STCS) for consistency and accuracy (Art. 20a). Since the STCS is mandated by the centers to comply with the legal obligations of post-transplant monitoring, the STCS and FOPH cross-check key transplant monitoring data on a yearly basis. According to Art. 20a 6, the DC receives once per year (since 2017) an extraction of SOAS data, is provided by BAG, data since January 2008 are included. We expect a 100% overlap of the SOAS numbers and of the data that are specified in Art. 20a. For each matching SOAS number the DC cross checks also the following information: age, gender, date of transplant and blood group. The comparison triggers a process of revision and feedback between the DC and the centers until the overlap is complete. *Genetic data* Genetic data concerns heritable individual's characteristics obtained from their genetic material (DNA) by genotyping or sequencing. Participation in genotyping and sequencing is evaluated based on STCS signed informed consent. Participants are informed about the nature of the research project, the way their genetic data is be collected, stored as well as which measures are be taken to protect their genetic data. Generated genetic data is tested for their quality by competent personnel in charge. Measure for quality control (QC) and accuracy of genetic data have been taken. It includes principal component analyses (PCs), sex determination, call rates, Hardy-Weinberg tests, homozygosity runs and imputation of measured SNPs to detect and exclude spurious effects of differential genotyping error. For

	additional control, internal audits may be planned. *Biological data (STCS Bio-banking)* Specific management involves the STCS bio-bank where the DC collaborates closely with the head and the operational manager of the STCS Biobank. The STCS runs a decentralized bio-bank with bio-banking of samples at each transplant center. Samples (plasma and viable cells at 0, 6 and 12 months follow-up, extracted DNA at time 0) are processed and stored according to the STCS bio-banking guideline and finally registered in the STCS DB by local site personnel. Upon SC and EC approval of a STCS NP that involves the STCS bio-bank, sample lists are generated according to the project protocol by the STCS DC. Once the list has been approved by the head of the bio-bank in collaboration with the operational bio-bank manager, it is sent to the local bio-bank (lab) at each involved center where the material can be retrieved and sent to the PIs under well-defined human material management, according to the ethical guidelines (www.stcs.ch). STCS LDMs check out the processed samples in the STCS DB by using the Sample Manager Tool. A copy of the requested sample list is stored at the DC for cross checking the samples retrieval and for reporting purposes. Lab audits and sample quality checks are done according to the STCS EO's and BOR's directive, in collaboration with the head of the STCS bio-bank. *Project-related data management* According to the requirements specified by a given STCS NP, customized data quality management and data processing are often needed. The STCS DC, as the primary data requests entry point collaborates and specifies with the project investigators the requirements for project specific data processing and/or data quality management. The DC moreover helps with existing data definitions, versioning of the data, and with the definition and linkage of "add-on" data that is potentially needed for a certain project, (https://www.stcs.ch/research/information-for-researchers). **1.2.3 Tools and Software** ● EVAT: Export validation tool ● DQMS: preprocessed data are selected and merged to test and report specific issues that address questions that have been raised by an online daily usage of the STCS DB, by previous queries or by planned periodical ad-hoc checks. Each extraction of the data is checked for completeness and consistency of several entries defined over time by quality and reporting questions. The so called query system is a repository of all scripts of checks run on each extraction and their outcomes. In addition the DC stores all issues addressed to the

	centers in csv or excel format and their feedback to be able to cross check the resolution of the issues. ● The ER Layer / analysis layer: is a tool that produced a set of tables based on preprocessed data with a relational data structure that contains all the data entered in the STCS application. The main difference to the data exported from the STCS application is the data structure and some additional variables (e.g. simult, resec, organ…) that can be derived. Introduced keys (unique identifier) will help that data can be safely merged in a flexible way. ● Metadata (STCS electronic codebook, eCB, see appendix B). A comprehensive web-based repository of all (non-genetic) past, current and planned data definitions used in the STCS DB. The eCB represents a key query interface that provides full versioning of all STCS variables and associated values. The technical framework of the eCB allows export of the eCB and serves as a data matrix for the data extraction validation, data processing and data quality management. The STCS ecodebook is machine readable (.csv exports and json exports available) ● Reporting tools for the STCS Annual Report and Data Quality Reports All analysis and data processing tools (EVAT, Analysis layer, Query tools) are implemented in SAS (Data Management and Advanced Analytics https://www.sas.com/de_ch/home.html) or R statistical software (The R Project for Statistical Computing, https://www.r-project.org/). *How will you organize your files and handle versioning?* All study documents are properly organized and securely stored within the file system of the STCS stored within the secure network of the University Hospital Basel. An evolving repository of guidelines, SOPs, and STCS reports are publicly available via https://www.stcs.ch/documents or via the STCS DC (https://www.stcs.ch/requests/submit-request, login needed). A comprehensive metadata system is in place and provides detailed specification and versioning of all variables, eCRFs (collections of variables), and data consistency rules (see STCS electronic codebook, section 1.3). The information stored in the metadata system can be exported and is used to implement format and consistency checks, checks for completeness, and validation of database exports.
1.3 What documentation and metadata will you provide with the data?	A comprehensive human and machine-readable metadata system (the STCS electronic codebook, eCB) is in place and represents the central repository of all non-genetic available data definitions that apply in the STCS. The eCB is an independent web-based platform hosted by SciCORE, that can be accessed after login. Users need to register via https://www.stcs.ch/contact/registration to receive

	their login after their role in relation to the STCS is verified through STCS personnel. Currently access is restricted to STCS members or to nested project investigators, but can be set user by user, independently from the role. The eCB is a complete electronic repository of all current, past and planned data definitions that apply in the STCS. All metadata content can be queried and exported (.csv or .json) and is thus fully machine-readable with the purpose to support data management, processing (see for example EVAT), and analysis. The eCB provides detailed specification of all non-genetic variables, formats, values, ranges, measures and units, used vocabularies, definitions and descriptions, eCRFs (collections of variables), and the mapping of variables into CRFs, dependencies of associated variables (records), and coherent classification of variables according to their content (e.g. all variables on renal transplant rejection, so called c ategories). Each variable is fully version controlled with validity ranges specified by start- and stop-dates for each version change. Naming conventions and version control are implemented for variables, CRFs, system releases, and export files (https://www.stcs.ch/data-portal/data-descriptions, requires a verified STCS account and login). *What community standards (if any) will be used to annotate the (meta)data?* FAIR speaks to the need to describe the conditions and processes for access and reuse after publication of discovered data. FAIR therefore requires to openly and richly describe the context within which those data were generated and to enable its evaluation of utility. FAIR is not equal to open. The concept of FAIR is superordinate to open data. As our cohort data are potentially sensitive (e.g. data sharing subject to consent, personal privacy of organ recipients and donors), they cannot be made freely open. The approach adopted in the STCS is to facilitate data reuse by making its metadata open, and by implementing a governance which allows distributing the actual data in a legally and ethically acceptable way. In the situation of the STCS, the FAIR approach can be applied to STCS nested projects (NP). The data of a NP corresponds to a snapshot i.e. a dataset of a given research project optionally enriched by "add-on" data. In this context, the FAIR principles can be applied. Findability: Register each NP at an open repository. Different repository choices must be carefully evaluated (e.g. dataverse@harvard.edu in line with the CTU Basel). Completion of the registration process by a research team will involve pushing the NP metadata to the repository and creation of a DOI persistent identifier for the metadata of the corresponding dataset. DOI reassures the long-term (at least 10 years) availability of the FAIRified dataset. The metadata are thus indexed in a searchable source. Accessibility: A user can openly access the metadata, will find the contact address and finds the requirements to request data for reuse

	(e.g. access control in case of sensitive data). To decide upon such reuse requests, a Data Access Committee (DAC) must be installed. For example, the STCS Scientific Committee or a subgroup thereof could adopt the role of the DAC and the STCS DC the role of the contact point of entry and the unit to manage reuse requests. Interoperability: Semantic interoperability is the sine qua non condition for any compliance with FAIR principles. In concrete terms, this means the mapping of the values in a STCS NP dataset to a well-known semantic structure that is findable and accessible such as a commonly used controlled vocabularies or ontologies. To comply with FAIR, the semantics of a FAIRified dataset will need to be published on the repository. Moreover, for each dataset, the atomic elements together with their persistent identifiers must be described. For the situation of the STCS the atomic structure is complex due to several interrelated data layers. Reusability: For the biomedical data of the STCS, the question of the data usage license is actually addressed via the ethical consent covered in the accessibility part.
2.1 How are ethical issues addressed and handled?	The STCS stores only pseudonymized (de-indentified) data within the STCS IT system hosted at sciCORE. The STCS considers all data as sensitive and therefore enforces the use of secure IT. Contracts (SLA) are in place to prevent non-authorized access to the data hosted at sciCORE. The STCS is conducted according to the ethical principles laid down in the Human Research Act (HRA), its Ordinance (HRO), according to the Declaration of Helsinki and Swiss legislation. Guidelines for Good Clinical Practice (GCP) are closely followed and any issue that arises is discussed with the authorities and organization of the STCS. Informed consent (IC) procedures are fully implemented in the STCS since the beginning and they are regularly updated if required by new legislation or novel developments within the STCS. Before the start of the cohort in May 2008 each transplant center obtained local Ethics Committee (EC) approval for general participation in the STCS, i.e. patients provide general written informed consent for the collection and use of full STCS data including bio-banking of samples. By the end of 2019, 93% of the 5672 Swiss transplant recipients provided written informed consent to the full STCS datasets (the other 7% having the minimal dataset required by law), and 99% of consenting patients contributed to the bio-samples. The STCS processes and provides only encoded data for research. Since 2014, medical research has been regulated comprehensively in Switzerland through the HRA/HRO. In 2016, STCS EC application procedures were centralized, with the “Ethikkommission Nordwest- und Zentralschweiz (EKNZ)” acting as the leading EC for the cohort. In order to comply with the new legislation a substantial regulatory amendment was prepared, in close collaboration with the Clinical Trial Unit (CTU) Basel, the EKNZ, the Swiss Biobanking Platform (SBP) and the Data Protection Officer Basel-Stadt. Formally the amendment

	was equivalent to a new project submission (research in persons, HRO Chapt. 2), with renewal of the complete study documentation. The STCS IC was updated and harmonized for all transplant centers. Where applicable, additional requirements for the consenting of particularly vulnerable patient groups were met, resulting in a total of seven population specific IC versions. After four years of preparation time the regulatory amendment was accepted on a national level in November 2019. Re-consenting of already enrolled participants was not requested by the EKNZ. With its entry into force in all transplant centers on January 1, 2020, the STCS fully complies with the Swiss legislations on human research. Coverage of STCS IC: the IC is covering the collection and further use for research of a) study participants' coded, health-related personal data and -samples, and of b) donor-derived data serving the donor-recipient matching and the assessment of organ quality and function. Add-on data and -biological material, produced as part of standard treatment, can be collected and further used for research in the context of a specific research project, based on the STCS IC and in compliance with the relevant legislation. Not covered by the STCS IC is the collection and further use for research of un-coded or anonymized data/samples. Interventional trials require an additional, study specific informed consent. Every STCS nested scientific project (NP) is subject to STCS Scientific Committee review and approval (www.stcs.ch) on its own. In accordance with the Human Research Act (HRA) and its Ordinance (HRO) each NP principle investigator must obtain project approval from the competent EC prior to releasing data for a specific project. The STCS transmits only coded data of consenting patients to researchers.
2.2 How will data access and security be managed?	Clinical data In 2019 and 2020 the STCS has entirely re-established its IT governance structure. All STCS applications were migrated to sciCORE BioMedIT node. The environment of highly secured STCS virtual servers is referred to as the STCS tenant. All web services are relayed through a proxy server located on the jump host. Only the encrypted protocol HTTPS is allowed. Access to web services are only be allowed from explicitly white-listed domains, in principle restricted to the five Swiss University hospitals contributing to the STCS network and designated associated organizations (e.g. Kantonsspital St-Gallen). The STCS management approves any modification to the white list. Given the limited network accessibility of the tenant, two-factor authentication is not required. Command-line access to the back-end systems is restricted to the developers of the STCS data management system and to the STCS management staff. The protocol to access the back-end is SSH. The physical infrastructure is located in an access-controlled data center managed by the central IT Services of the University of Basel (IT-S), the sciCORE/BioMedIT racks are locked and accessible only by

	the sciCORE personal required for maintenance. sciCORE partially relies on an offsite backup infrastructure located in another access-controlled data center at FHNW Muttenz, (under IT-S governance). Backups to this secondary site are encrypted at the source. The system hosted at SciCORE benefits from the following security framework: • All web services are relayed through a proxy server located on the jump host. Only the encrypted protocol HTTPS is allowed. • Access to web services is only be allowed from explicitly white-listed domains, in principle restricted to the 5 Swiss University hospitals contributing to the STCS network and designated associated organizations (e.g. Kantonsspital St-Gallen). The STCS management approves any modification to the white list. • Given the limited network accessibility of the tenant, two-factor authentication is not required. • Command-line access to the back-end systems is restricted to the developers of the STCS data management system and to the STCS management staff. The protocol to access the back-end is SSH. Genetic data Individual's genetic data is stored in the controlled-access database on HPC server or ACAD-NAS. The genetic data can be accessed with a personal login and password according to the Institutional rules. The service provides appropriate protection of the hosted data on its technical infrastructure including the confidentiality and integrity of the data. The Institution does not modify or transmit the data. Robust technical and administrative security measures are in place to protect against unauthorized access, accidental or illegal destruction or modification of genetic data in the central database. The access to genetic data is logged and protected by security password. Password enforcement rules apply for each user of genetic database at HPC or ACAD-NAS and the active directory requires the users to change their password regularly.
2.3 How will you handle copyright and Intellectual Property Rights issues?	Who will be the owner of the data? The STCS together with all participating centers own the data. Which licenses will be applied to the data? None. What restrictions apply to the reuse of third-party data? The STCS Scientific committee and the competent Ethic Committee must revise and approve on all proposals for reuse of third party. Authorship and publication The procedure described in the SWISS TRANSPLANT COHORT STUDY GUIDELINES AND OPERATIONAL RULES FOR SCIENTIFIC

	PROJECTS applies (https://www.stcs.ch/research/information-for-researchers).
3.1 How will your data be stored and backed-up during the research?	Clinical data The primary data storage is within the STCS database hosted at SciCORE. The secured tenant consists of: ● A private virtual network ● 2 Linux virtual machines to host the development and production instances of the STCS data management system. ● Associated storage system The following technical measures related to security are applied: ● All web services are relayed through a proxy server located on the jump host. Only the encrypted protocol HTTPS is allowed. ● Access to web services is allowed only from explicitly white-listed domains, in principle restricted to the 5 Swiss University hospitals contributing to the STCS network and designated associated organizations (e.g. Kantonsspital St-Gallen). The STCS management approves any modification to the white list. ● Given the limited network accessibility of the tenant, two-factor authentication is not required. ● Command-line access to the back-end systems is restricted to the developers of the STCS data management system and to the STCS management staff. The protocol to access the back-end is SSH. Backup procedures: ● The VMs in the tenant undergo daily incremental backups to an NFS file share. Backups are then stored offsite using an encrypted tape infrastructure. Different versions of the backup can be recalled with a version history of up to 90 days. ● The Gitlab service is backed up offsite, with a retention history of 90 days. Raw data exports are stored with the STCS DC as plain text files. Processed data are stored as sas-files, csv-files and text files within the STCS DC and distributed to end users (researcher) via a password-protected web interface (www.stcs.ch). All files stored at DC are located within the host high performance computing (HPC) server at the USB (University Hospital of Basel) in a secured computer environment within dedicated space accessible only by authorized members of the STCS the DC. Sas-, csv-, text-, and specific program files together with the appropriate program code for projects and reports are preserved within the secured IT systems of USB (DC), SciCORE and regularly backed-up. Genetic data The genomic data is stored in the high-performance computing

	cluster of the Lausanne University Hospital (CHUV), the genotype data are in plink and the imputed data are in bgen format. The cluster is located in the academic data center of the academic network of the CHUV (acad-net). The Academic Data Center (ACAD-DC) and it is reachable only from ACAD-net, the CHUV clinical network and some users from the University of Lausanne (UNIL). In order to use the HPC or ACAD-NAS resources, users must be authenticated by the Active Directory of the CHUV-IT. The allowed protocols to access HPC are http, https and SSH. The active directory requires the users to change their password regularly. Other password enforcement rules are also applied. Partners who signed an NDA (Non Discloser Agreement) may also access resources hosted in the ACAD-Net and ACAD-DC using VPN connection and each VPN connection is logged. Data is backed up on a NAS server on the same network. Only members of the group of Prof Kutalik have access to the data.
3.2 What is your data preservation plan?	What procedures would be used to select data to be preserved? The STCS is an open cohort study without a pre-specified end of study. Project specific data are stored by the investigator and the STCS Data Center together with the appropriate analysis code. The full data for the STCS Annual report is stored together with the report and the corresponding analysis code. What file formats will be used for preservation? Clinical data Sas-, csv-, text-, and specific program files together with the appropriate program code for projects and reports are preserved within the secured IT systems of USB (DC), SciCORE and regularly backed-up. Genetic data The entire individual's genetic data is encrypted and stored either as PED/MAP files (PLINK format) and GEN files (IMPUTE format). This genetic data will be separated from sensitive data (e.g. health data). All files that need to be backed up will be stored at ACAD-NAS or NAS-UNIL in a dedicated space accessible only by authorized members of the STCS genetic group. The ACAD-NAS will be backed up by snapshots, which are saved on different remote locations. In order to use genetic data from HPC or ACAD-NAS/NAS-UNIL resources, users must be authenticated by security staff (CHUV Active Directory).
4.1 How and where will the data be shared?	On which repository do you plan to share your data? SBP eCatalogue, other repositories are under evaluation. How will potential users find out about your data? The STCS is a nationally and internationally well-recognized tool for post-transplant outcome research. Investigators propagate the STCS as an open-access tool during conferences and meetings. The STCS website (www.stcs.ch) provides all information for researchers to collaborate with the STCS. A growing body of scientific publications

	on national and international collaborations moreover propagate the STCS as an open tool for research. The transplant research community within Switzerland is closely linked to the STCS, therefore, new interested parties and young researchers are easily connected to the cohort via the transplant centers. The STCS applicants are also very active internationally, thus promoting the cohort beyond Switzerland, which leads to interest and requests for use of the data in international projects. In order to grant the correct and secure use of STCS data, all projects (national and international) undergo the review process of the STCS Scientific Committee and are registered as nested projects, regardless of whether they apply for STCS funding dedicated to STCS nested projects or not. Initial requests for information are handled through the website, which provides a detailed description of the data and samples available. For those researchers wishing to submit, the process is delineated in detail, with support from the Scientific Committee if necessary. Importantly, and to promote research and use of data, for MD and master thesis a simplified procedure is in place. Current STCS data access and publication policy: STCS data is open to external researchers as stated on the project website (www.stcs.ch). The publicly accessible section "Information for researchers" explicitly states that all types of research projects related to transplantation are welcome and that every scientist is invited to submit research projects. Projects are subject to review by the Scientific Committee (SC) of the STCS. The review process is transparent and follows defined guidelines. Since May 2016, all newly accepted STCS research projects must obtain EC approval. The STCS is compliant with the Swiss National Science Foundation (SNSF) obligation for Open Access publishing and implemented the "Green road of Open Access" in 2017. PIs are working on data releases uploaded in the website and officially released by the DC.
4.2 Are there any necessary limitations to protect sensitive data?	The STCS is required to record and store the date of birth (DOB) of the recipient and the donor for the following reasons: 1. The DOB is of key importance for patient identification and quality assurance in the context of NPs that are in need of add-on data collection or data linkage 2. For studies on pediatric TX recipients. lt is important to note that, in order to comply with the guidelines of Swissethics on the encoding of a person-related health data, the STCS replaces each DOB by the year of birth and the age during the processing of research data. Hence, the date of birth is not passed on to researchers unless the competent ethics committee has explicitly approved this for a specific NP.