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Basel Long COVID Cohort Study (BALCoS): protocol of a prospective cohort study

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ABSTRACT

Introduction The recent pandemic caused by SARS-CoV-2 had a profound global impact. While many individuals recovered from COVID-19, some developed long-lasting symptoms that significantly disrupted daily life. The WHO defines this condition as post-COVID-19 condition (PCC). Common symptoms include fatigue, dyspnoea, sleep disturbances and cognitive difficulties. Increasing evidence suggests that PCC is a multifactorial condition, shaped not only by biomedical but also psychological and social factors. This article presents the protocol of the Basel Long COVID Cohort Study (BALCoS), which aims to improve understanding of PCC by capturing clinical, functional and psychosocial aspects through repeated assessments over the course of 1 year.

Methods and analysis BALCoS is a prospective, single-site cohort study. Inclusion criteria include either a probable or confirmed history of SARS-CoV-2 infection with persistent symptoms consistent with the WHO definition of PCC, sufficient German language skills and age ≥18 years. At baseline, we collected detailed information on previous SARS-CoV-2 infections, symptom history, reinfections, COVID-19 vaccination status and pre-existing medical conditions. The study includes standardised psychometric assessments, physical performance tests, ecological momentary assessments (EMAs), neurocognitive testing and blood sample collection. Assessments are scheduled at baseline and at 3-month, 6-month and 12-month follow-up. All participants complete psychometric assessments at each time point. Blood samples are only collected at baseline. Neurocognitive testing and physical performance measures are collected at baseline and 12-month follow-up for in-person participants only. Participants who are unable to attend in person complete a remote version of the study, excluding these in-clinic assessments. EMAs are initiated the day after each time point and consist of eight questions over 10 consecutive days. The study is exploratory in nature, with a target sample size of 120 participants. BALCoS is part of the Horizon Europe Long COVID project, a multinational interdisciplinary research consortium integrating mechanistic, clinical and interventional studies.

Ethics and dissemination The study was approved by the Ethics Commission of Northwest and Central Switzerland (BASEC-ID: 2023–00359) and is registered at ClinicalTrials.gov (ID: NCT05781893). All participants provide written informed consent. Study findings will be disseminated through peer-reviewed publications.

Trial registeration number NCT05781893.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study includes both clinical and psychosocial dimensions of post-COVID-19 condition (PCC), incorporating standardised instruments for anxiety, depression, somatic distress and work ability.

⇒ Repeated assessments using a wide range of validated, participant-reported outcome measures provide real-world insight into symptom trajectories, illness course, functional impairment and quality of life.

⇒ Retrospective assessment of preinfection symptom history allows contextualisation of PCC changes and supports identification of new or exacerbated symptoms.

⇒ As an exploratory observational study, the Basel Long COVID Cohort Study enables the identification of potential associations and risk factors but does not allow for conclusions regarding causality.

⇒ Gathering SARS-CoV-2 infection status via participant self-report rather than through standardized testing seems limiting, but it realistically reflects diagnostic practices in clinical settings and accurately represents the patient population presenting to specialised PCC clinics.

INTRODUCTION

In early 2020, COVID-19, caused by SARS-CoV-2, led to a global pandemic. As the pandemic progressed, it became apparent that the disease not only causes acute symptoms but can also lead to long-term complaints. These persistent symptoms—often referred to as 'long covid' and hereafter termed 'post-COVID-19 condition' (PCC)—can have significant effects on daily functioning.

According to the WHO, PCC is defined as symptoms that persist for at least 2 months and typically begin within 3 months after a confirmed or probable SARS-CoV-2 infection, and cannot be explained by an alternative diagnosis.[1] Symptoms are heterogeneous[2] and can affect multiple organ systems. Commonly reported complaints include fatigue, dyspnoea, sleep disturbances, persistent cough, anosmia or ageusia, chest pain and headaches.[3] Prevalence estimates vary depending on study design, population and diagnostic criteria. A 2022 meta-analysis reported a prevalence of 7.5% to 41% in non-hospitalised adults, and an average of 37.6% among hospitalised patients.[4] Due to methodological differences in the published literature, prevalence rates vary considerably, and numbers are difficult to reliably estimate.

Although several risk factors have been identified, such as virus variant, female sex, hypertension, obesity, smoking and pre-existing comorbidities,[5–9] the underlying mechanisms of PCC remain poorly understood.[10 11] Various hypotheses have been proposed, including immune dysregulation,[12] persistent viral reservoirs or microbiota dysbiosis,[13] autoimmunity and primed immune cells by molecular mimicry,[14] endothelial dysfunction[15] and altered neurophysiological signalling.[16] While biomedical mechanisms remain a primary focus, PCC is increasingly recognised as a complex, multifactorial condition. Psychological, social and behavioural factors have also been shown to influence both symptom severity and illness persistence.[17] These insights inform the development of integrated, patient-centred care models and underline the need for a more holistic understanding of the condition.[18] Due to the limited understanding of PCC pathogenesis, current treatment strategies primarily aim at symptom management. This lack of clarity may contribute to the psychological burden experienced by affected individuals, including frustration, helplessness, uncertainty about disease course and reduced sense of control.[19] A better understanding of PCC—including its biological, psychological and social determinants—could support the development of effective care strategies and improve outcomes for those affected.[20 21]

Study objectives

This protocol outlines the Basel Long COVID Cohort Study (BALCoS), which aims to investigate and improve the understanding of PCC, its clinical manifestations, symptom trajectories and underlying multifactorial mechanisms. The study is prospective and observational in design and captures data at baseline and 3 months, 6 months and 12 months.

The study focuses on the following core objectives:

- Characterisation of clinical presentations and symptom patterns of individuals with PCC.
- Description of demographic, clinical and laboratory profiles of affected individuals, including detailed information on prior SARS-CoV-2 infections and reinfections, vaccination status, pre-existing medical conditions and retrospectively assessed symptom history prior to infection.
- Identification of potential risk factors for the development and persistence of PCC (eg, age, sex, comorbidities).
- Longitudinal evaluation of symptom trajectories and functional outcomes over time.
- Assessment of the impact of PCC on health-related quality of life, psychosocial well-being, functional status and work ability.
- Analysis of prior treatment experiences, healthcare utilisation and potential unmet care needs in individuals with PCC.

While the study is exploratory in nature and does not aim to test predefined hypotheses, it is guided by the following central assumptions:

- Individuals with PCC exhibit distinct clinical and psychosocial profiles compared with their pre-infection state.
- Certain demographic and clinical characteristics (eg, female sex, pre-existing conditions) are associated with a higher risk for developing or maintaining persistent symptoms.
- PCC has a measurable negative impact on quality of life, functional ability and work capacity that might change over time.

Assessment methods and definition of PCC severity

To capture the complex and multidimensional nature of PCC, participants undergo a comprehensive assessment protocol including validated questionnaires, neurocognitive testing, physical performance measures, ecological momentary assessments (EMAs) and biomarker analyses. Data collection occurs at multiple time points over a 1 year period, enabling analysis of the course of symptoms and functional status over time. Given the absence of a single diagnostic test or biomarker to quantify PCC severity, we conceptualise severity as a composite of functional and symptomatic impairment. This is assessed through changes in standardised instruments, such as the WHO Disability Assessment Schedule 2.0 (functional ability), the Patient Health Questionnaire (somatic symptom severity) and the Somatic Symptom Disorder – B Criteria Scale (somatic distress based on DSM-IV criteria). Variations in these scores over time serve as indicators of change in symptom burden. In addition, physical performance is evaluated using objective functional tests, including the 6 min walk test and handgrip strength assessment.

METHODS AND ANALYSIS

Study design and setting

BALCoS is a registry-based, single-centre, prospective, observational cohort study. It is conducted at the Medical Outpatient Clinic of the University Hospital Basel (UHB). Participants are recruited from patients attending the hospital's specialised PCC consultation service. In addition, participation is open to individuals referred from external clinics or consultation services, as well as to those responding to public study advertisements. Written informed consent is obtained from all participants.

Study timeline

Recruitment began in February 2023, with the first participant enrolled in April 2023. The study is designed

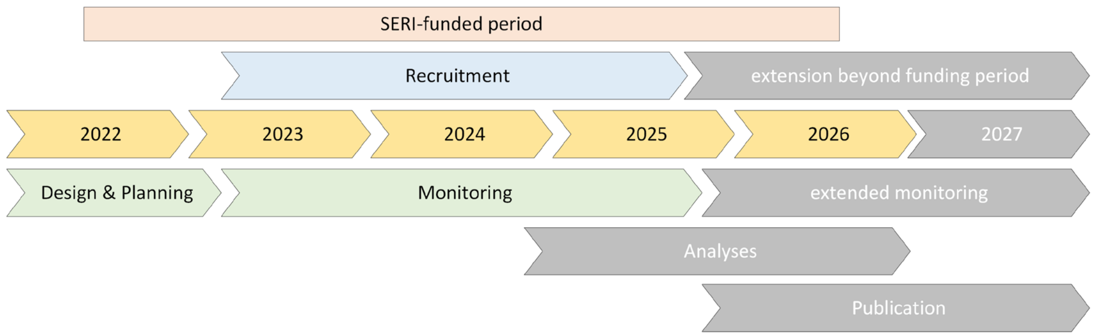

Figure 1 Timeline of the Basel Long COVID Cohort Study. SERI, State Secretariat for Education, Research, and Innovation.

to continue beyond the currently funded research period (supported by the State Secretariat for Education, Research and Innovation until May 2026) to allow for ongoing data collection, longitudinal analyses and continued investigation of the research questions, including the evolution of PCC over time (see figure 1).

Since the start of recruitment, protocol amendments have addressed procedural aspects only—specifically the recruitment strategy, the duration of the recruitment phase and the inclusion criteria. Protocol amendments are described in detail in the Sampling procedure section.

Study schedule

Participants are asked to provide informed consent for the inclusion of relevant prior medical data that may relate to their PCC symptoms. They are also asked to agree that data collected during the study may be used to inform routine clinical care. Participants not recruited from the PCC clinic at UHB provide this information during an entry interview, after signing the informed consent form. An overview of all clinical data collected through interviews and routine examinations is provided in the online supplemental material.

Study assessments are scheduled at four timepoints: at baseline (BL) and at 3 months (T1), 6 months (T2) and 12 months (T3) after baseline.

For participants attending in person, psychometric assessments are conducted digitally (eg, via tablet or computer) at all four timepoints. Neurocognitive testing and physical performance measures are conducted at BL and repeated at T3. Blood samples are collected at BL only. If the baseline assessment is too exhausting to complete in one visit, a second appointment can be arranged to complete the neurocognitive and physical performance components (as marked with '(x)' in table 1).

Participants may choose to complete the study remotely if travel to the study site is not feasible due to health concerns or symptom burden. In this case, neurocognitive testing, physical performance measures and blood sampling are omitted, but psychometric questionnaires and EMAs are completed as scheduled.

All participants, regardless of recruitment type, complete the psychometric assessments for T1 and T2 at home using personalised links sent via email. T3 may also be completed remotely if a site visit is not possible.

EMAs are used to capture daily symptom fluctuations and contextual factors in real time. All participants complete the EMAs remotely. Starting 1 day after each study timepoint (BL, T1, T2, T3), participants receive a daily text message at 18:00 with a link to a set of eight brief questions. These questions are answered once daily over a period of 10 consecutive days.

A detailed overview of the study schedule is provided in table 1.

Sampling procedure and selection

Participants are enrolled based on predefined inclusion criteria (see table 2). Recruitment is conducted by members of the study team, including physicians, psychologists, psychotherapists and study nurses.

Initially, until June 2024, only patients attending the PCC clinic at UHB were recruited. Due to slower-than-expected enrolment, the recruitment strategy was expanded in July 2024 to include individuals from other specialised consultation services and clinics in the Basel area, provided they had a physician-based diagnosis of PCC. Since September 2024, individuals with persistent symptoms consistent with PCC and a subjective attribution of their symptoms to a prior SARS-CoV-2 infection are also eligible for inclusion. The inclusion criteria were adapted in response to evolving national testing strategies, as SARS-CoV-2 testing during the acute phase was no longer routinely recommended or reimbursed. Consequently, we allowed for the inclusion of individuals with either a probable or confirmed history of SARS-CoV-2 infection, in alignment with the WHO definition of PCC.

The study is advertised through various channels, including specialised and general outpatient clinics, general practitioners' offices, public transportation, academic conferences and symposia, mailing lists and social and digital media. All potential participants are screened for eligibility according to the predefined inclusion and exclusion criteria.

Written informed consent is obtained by a study investigator or designated team member. If participants are unable to attend in person for the purpose of the consent process, study information is presented via phone or video call. During the consent process, participants are informed about the study's purpose, procedures, expected duration, potential risks and benefits and their

Table 1 Outcome measures and assessment schedule

	Outcome measure	BL 1	BL 2	T1	T2	T3
0	Oral and written information, written consent, screening of inclusion and exclusion criteria	x				
1	Blood samples*	x				
2	Neurocognitive assessment: Central Nervous System Vital Signs *	x	(x)			x
3	Physical performance measures*					
a	6 min walking test	x	(x)			x
b	Jamar dynamometer	x	(x)			x
c	1 min sit-to-stand test	x	(x)			x
4	Psychometric questionnaires					
a	Functional Capacity: WHO Disability Assessment Schedule	x		x	x	x
b	Visual Analogue Scales: quality of life, symptom intensity, functional impairment, work ability	x		x	x	x
c	Quality of Life: Quality-of-Life-8 (EuroHIS)	x		x	x	x
d	Somatic symptom severity: Patient Health Questionnaire	x		x	x	x
e	Somatic Distress: Somatic Symptom Disorder – B Criteria Scale	x		x	x	x
f	Depression : Patient Health Questionnaire Depression Scale	x		x	x	x
g	Anxiety: Generalised Anxiety Disorder Questionnaire	x		x	x	x
h	Resilience: Resilience Scale	x		x	x	x
i	Insomnia: Insomnia Severity Index	x		x	x	x
j	Fatigue : Chalder Fatigue Scale	x		x	x	x
k	Stress: Perceived Stress Scale	x		x	x	x
6	Ecological momentary assessments (eight daily questions for 10 consecutive days after BL, T1, T2, T3)		x	x	x	x

*Measurements not completed by remote participants.
BL, Baseline; T1, 3 months after Baseline; T2, 6 months after Baseline; T3, 12 months after Baseline.

right to withdraw at any time without consequences for their future medical care.

No formal sample size calculation or power analysis was performed prior to recruitment due to the exploratory nature of the study. The target sample size of 120 participants during the funded period is based on feasibility estimates derived from the number of individuals who sought help at the PCC clinic in 2021 and 2022.

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Confirmed or probable history of SARS-CoV-2 infection with persistent symptoms consistent with the WHO definition of post-COVID-19 condition	Lack of sufficient understanding of the study procedures
Age ≥18 years	Refusal to provide written informed consent
Adequate knowledge of German to understand and complete study procedures	

SARS-CoV-2, Severe acute respiratory syndrome Coronavirus 2; WHO, World Health Organization.

Horizon Europe long covid consortium

The BALCoS study is conducted within the framework of the Horizon Europe Long COVID consortium. This interdisciplinary and international research network was established in response to a European Union funding initiative, with the overarching aim of advancing the understanding of PCC, elucidating its underlying mechanisms and contributing to the development of improved healthcare strategies. The consortium coordinates a broad range of studies across multiple countries, employing diverse research methodologies. Collaboration within the consortium includes structured data and biosample sharing. In this context, selected blood samples and analytical results obtained in BALCoS are made available to partner research groups within the consortium to support joint research objectives.

Table 3 Overview of blood sample collection

Blood samples for potential future analyses	Blood samples for the consortium	Routine clinical care
RNA tubes for genetic analyses (optional)	EDTA plasma (for genetic analyses; optional)	See laboratory parameters in the supplemental material
EDTA plasma	Citrated plasma	
Serum	Serum	

EDTA, Ethylenediaminetetraacetic Acid; RNA, Ribonucleic Acid.

Blood samples and assessments

Blood samples

As part of routine clinical care, patients attending the specialised PCC clinic at UHB undergo standard blood testing. The results of these tests, including blood count, inflammatory markers and liver and kidney function, are extracted from the hospital records and entered into the study database (see the laboratory parameters in the online supplemental material). In addition, participants provide study-specific blood samples at BL for selected analyses conducted in partner laboratories within the consortium (see table 3). These external analyses include (a) genomic and human leucocyte antigen typing (plasma), (b) COVID-19 antibody profiling (serum), (c) lipidomic profiling (serum), (d) characterisation of autoantibody epitopes (serum) and (e) coagulation markers (citrated plasma). Due to resource constraints, some of these analyses are performed only on a subsample of study participants. Importantly, participation in the study is not contingent on consent to genetic analyses; participants may decline this component and still take part in the broader study. Additional blood samples were collected and frozen for potential future analyses, provided that participants had given their consent.

Neurocognitive testing

Central Nervous System Vital Signs (CNSVS,[22]) is a computerised neurocognitive test battery developed for routine clinical screening. It comprises seven scientifically validated and reliable neuropsychological subtests: verbal memory, visual memory, finger tapping, symbol digit coding, Stroop test, shifting attention test and continuous performance test. The battery takes approximately 40–50 min to complete.

The psychometric properties of the CNSVS subtests have been shown to be comparable to those of conventional, interview-based neuropsychological assessments from which they were originally derived.[23]

Psychometric questionnaires

Visual Analogue Scales (VAS[24])*:* Participants answer four questions on a VAS with a 10-point scale ranging from 1 to 10. The questions cover symptom intensity ('How do you currently rate the intensity of your symptoms?', 10=it can't be worse), functional impairment ('How do you currently rate the impairment caused by your symptoms in everyday life?', 10=it can't be worse), quality of life ('How would you rate your current quality of life?', 10=it can't be better) and work capacity (10=full work capacity). For work capacity, participants indicate their current work capacity ('current workload in % per week') and their maximum work capacity before the onset of PCC symptoms on a scale from 0% to 100% ('regular workload before symptoms started in % per week').

Functional Capacity – WHO Disability Assessment Schedule (WHODAS 2.0): The WHODAS 2.0 assesses and classifies disability due to health problems during the four previous weeks. The 12-item version is used in this study.[25] An example item would be 'In the past 4 weeks, how much difficulty have you had walking a long distance such as 1 km (or equivalent)?'. Items are answered on a 5-point Likert scale ranging from 0 = 'none' to 4 = 'extreme or impossible'.

Quality of Life – EuroHIS Quality-of-Life-8[26]: This 8-item instrument assesses quality of life and perceived health during the four previous weeks, for example, by asking, 'Do you have enough energy to cope with everyday life?'. Items are answered on a 5-point Likert scale, with wording varying between questions (eg, from 'very dissatisfied' to 'very satisfied').

Somatic Symptom Severity – Patient Health Questionnaire (PHQ-15[27]): the PHQ-15 assesses the severity of somatic symptoms over the previous 4 weeks. Participants are asked how much they felt affected by their symptoms (eg, back pain). Items are answered on a 3-point Likert scale ranging from 0 = 'not bothered at all' to 2 = 'bothered a lot'.

Somatic Distress: Somatic Symptom Disorder – B Criteria Scale (SSD-12, [28]): the SSD-12 assesses psychological features of somatic disorders with four questions each on the cognitive (disproportionate and persistent thoughts about the seriousness of one's symptoms), affective (health anxiety) and behavioural (excessive time and energy devoted to these symptoms or health concerns) dimensions. Items are answered on a 5-point Likert scale ranging from 0 = 'never' to 4 = 'very often'.

Depression – Patient Health Questionnaire Depression Scale (PHQ-8[29]): the PHQ-8 assesses the severity of depressive symptoms according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV[30]). Participants are asked whether they have been bothered by symptoms typical for depression (eg, by having little interest or pleasure in doing things) in the past few weeks. Items are answered on a 4-point Likert scale ranging from 0 = 'not at all' to 3 = 'almost every day'.

Anxiety – Generalized Anxiety Disorder Questionnaire (GAD-7[31]): the GAD-7 measures anxiety. It assesses whether the participant has been bothered by complaints related to anxiety in the past 2 weeks (eg, by asking about difficulties in relaxing). Items are answered on a 4-point Likert scale ranging from 0 = 'not at all' to 3 = 'almost every day'.

Resilience – 11-item Resilience Scale (RS-11[32]): the RS-11 asks about general resilience to life events, for example, 'I feel that I can handle many things at the same time.' Items are answered on a 7-point Likert scale ranging from 1 = 'strongly agree' to 7 = 'strongly disagree'.

Insomnia – Insomnia Severity Index (ISI[33]): the ISI assesses sleep problems. Items are answered on a 5-point Likert scale regarding severity over the past 2 weeks, with wording varying between questions (eg, from 0 = 'very dissatisfied' to 4 = 'very satisfied').

Fatigue – 11-item Chalder Fatigue Scale (CFS[34]): the CFS assesses fatigue on a mental subscale (eg, by asking 'Do you have difficulty concentrating?') and a physical subscale (eg, by asking 'Do you need to rest more?'). Items are answered on a 4-point Likert scale ranging from 0 = 'better than usual' to 3 = 'much worse than usual'.

Stress – Perceived Stress Scale (PSS-10[35]): the PSS-10 assesses the experience of psychological stress in the last 4 weeks. It consists of 10 items, for example, 'In the last month, how often have you been upset about something that happened unexpectedly?'. Items are answered on a 5-point Likert scale ranging from 1 = 'never' to 5 = 'very often'.

EMA Questions – After each data collection point (BL, T1, T2, T3), participants answer eight daily EMA questions for 10 consecutive days. Questions 1–5 are based on the Screening Tool for Psychological Distress,[36] question six is based on the European Quality of Life 5 Dimensions,[37 38] question seven is based on the Single Item Mindfulness Scale[39]39 and question eight is based on the Single Item Self Compassion Scale.[40] The questions are completed in the Research Electronic Data Capture (REDCap[41]) on a 10-point Likert scale ranging from 0 = "not at all" to 9 = "severely". The eight questions are phrased as follows: 'In the last 24 hours, how much have you been…'

1. …bothered by feeling sad, down, or uninterested in life?
2. …bothered by feeling anxious or nervous?
3. …bothered by feeling stressed?
4. …bothered by feeling angry?
5. …bothered by not having the social support you feel you need?
6. …bothered by difficulties in carrying out your daily activities?
7. …fully in the moment, accepting it as it is?
8. …experienced high levels of self-compassion?"

Measures of physical performance

Grip strength – Jamar dynamometer[42]: participants are seated in a chair and instructed to squeeze a hydraulic grip strength dynamometer with one hand while the other arm rests on their lap. The test is performed three times per hand, starting with the dominant hand. The best value (in kg) for each hand is recorded. Any injuries to one or both hands are documented.

Functional exercise capacity – 6 min walking test[43]: the total distance (in metres) a participant walks in 6 min is recorded. Pulse and oxygen saturation are measured at BL, immediately after the test, and again 2 min post-test using a pulse oximeter. Participants rate their subjective well-being before and after the test on a 5-point Likert scale (1 = 'very poor' to 5 = 'very good'). In addition, perceived respiratory and leg exertion are assessed post-test using the Borg Category-Ratio (CR) 10 Scale (0 = 'no exertion' to 10 = 'maximum exertion').[44]

Muscular endurance – Sit-to-Stand Test (STS-60[45]): the STS-60 assesses lower-body muscular endurance by counting how many sit-to-stand repetitions participants can perform in 60 s without using their hands for support. Oxygen saturation is measured at the end of the test using a pulse oximeter.

Data collection and management

Data are primarily collected through electronic means. Psychometric questionnaires, EMAs and neurocognitive assessments are administered via online surveys or computerised test formats. Physical performance data are collected using paper-based forms. Electronic data capture is conducted using the REDCap electronic case report form. Paper-based data are manually entered into REDCap by trained study personnel.

Clinical data are retrieved either from the patient's medical records or, in the case of externally recruited participants, obtained during a structured clinical entry interview conducted by the study team. These data are then transferred into REDCap.

Data quality is ensured through ongoing monitoring, plausibility checks and validation of missing values by trained data managers. Participants receive automated reminders from REDCap to complete their psychometric questionnaires at T1 and T2, 3 days and 7 days after the initial invitation. If questionnaires remain incomplete, participants are contacted by phone 2 weeks after the initial reminder.

EMA adherence is monitored manually by the study team. If two consecutive EMA entries are missed, participants are contacted to encourage continued participation.

Data management and monitoring are performed exclusively by authorised and experienced study investigators and project staff. In accordance with local laws and regulations, health-related data and biological materials are stored for 10 years after publication of the research results. All electronic documents are stored on secure servers maintained and regularly backed up by UHB.

As early as possible after data collection, study-related documents are pseudonymised, and participants are identified solely by a unique participant ID. Personal data (eg, phone numbers and email addresses) are recorded in REDCap solely for the purpose of distributing psychometric questionnaires and EMA links at T1 and T2. Any personal or study-related data are accessible only to authorised personnel; paper-based documents are stored in locked offices.

All study team members involved in data collection, monitoring or the use of specialised software have been trained by senior team members and/or have completed a formal training programme. All procedures follow Standard Operating Procedures issued by UHB or developed by the study team in accordance with Good Clinical Practice guidelines.

Statistical analyses

All data will be analysed using established statistical software, such as R within RStudio.[46] We will present descriptive statistics as follows: categorical variables will be summarised using counts and percentages, while continuous variables will be summarised as means±SD or medians with IQR, depending on the distribution as assessed by visual inspection (histograms, Q-Q plots) and formal tests (eg, Shapiro-Wilk). Longitudinal changes in psychometric, neurocognitive and physical-performance outcomes at BL, T1, T2 and T3 will be assessed using generalised linear mixed models. Fixed effects will include time as the main factor of interest, with demographic characteristics (eg, sex, age) and selected baseline clinical variables (eg, duration of PCC symptoms, comorbidities) included as covariates to adjust for potential confounding where appropriate. Random intercepts, and possibly random slopes for time, will be incorporated to account for repeated measures within participants. Model assumptions will be examined using residual diagnostics, and model selection will be informed by the Akaike Information Criterion and Bayesian Information Criterion. To investigate if key demographic or clinical variables modify trajectories over time (effect modification), we will test predefined interaction terms individually (eg, time×sex, time×age category, time×symptom duration category). Significant interaction effects will be explored using estimated marginal means to visualise symptom trajectories across different strata. Separate subgroup analyses are not planned as a primary approach. EMA data will be analysed using generalised additive mixed models, incorporating smooth functions of time to capture non-linear patterns and fluctuations in symptoms over the study period. EMA models will consider serial autocorrelation within participants. We will also conduct correlation analyses between aggregated EMA scores and corresponding psychometric questionnaire scores to explore associations between real-time and retrospective symptom reporting. Exploratory analyses may additionally include examination of other potentially relevant clinical predictors of outcomes, contingent on data availability and sufficient sample size. Any such analyses shall be identified as exploratory. Sensitivity analyses will be considered where appropriate to examine the robustness of the results, for instance, by excluding remotely recruited participants or applying alternative analytical approaches. Missing data patterns will be examined, and appropriate imputation methods (eg, multiple imputation) will be applied if required. Missing data are categorised into three groups: drop-out, lost-to-follow-up and discontinuation. Drop-out is defined as clear, participant-initiated, written or verbal withdrawal of consent before they complete the last data collection point (T3), in which case recorded participant data are deleted on request. Participants who withdraw from the study cannot be re-enrolled at a later time. Participants are discontinued from the study if they are not reachable and/or refrain from communicating with the study team before any data collection. In case any data were collected (eg, blood samples from BL), they are declared lost to follow-up. Missing data from discontinued participants will not be imputed. Participants are contacted up to four times before being considered lost to follow-up or discontinued. The contact sequence includes two phone attempts (with voicemail messages), and one final email notification. If no response is received, and no data have been collected, the participant is classified as discontinued. If some data were obtained (eg, blood samples at baseline), the case is considered lost to follow-up.

ETHICS AND DISSEMINATION

The study has been approved by the Department of Clinical Research at UHB (ID: th22schaefert) and the Ethics Commission of Northwest and Central Switzerland (ID: 2023–00359) and is registered at ClinicalTrials.gov (ID: NCT05781893).

The first amendment to this study protocol was submitted to the local ethics committee on 18 March 2024 and approved on 22 March 2024. A second amendment was submitted on 3 June 2024 and approved on 18 June 2024. Any future amendments will be submitted to the appropriate regulatory bodies as required.

The results of the BALCoS study will be published in peer-reviewed scientific journals. In addition, findings will be presented at conferences, symposia, lectures and public outreach events. The full study protocol is made accessible through this manuscript. BALCoS results will also feed into Horizon Europe Long COVID consortium (see section 'The Horizon Europe long covid consortium') publications and shared dissemination efforts.

Authorship eligibility for this publication follows the criteria established by the International Committee of Medical Journal Editors.[47]

Risks and harm to participants

Participation in the study involves no interventions beyond standard medical care. No radiation is used, and no vulnerable populations are specifically targeted. The only additional burden for participants arises from the collection of study-specific blood samples and the detailed data collection, which may require cognitive effort and time.

Participants receive a compensation of 50 Swiss Francs on completion of the T3 follow-up. In the event of early withdrawal, a proportional amount is reimbursed based on completed study visits.

According to the Swiss Human Research Ordinance (HRO, Art. 7), the study is classified as risk category "A". Adverse events and serious adverse events will be reported in accordance with HRO Art. 21. Any safety-related measures will be reported to the relevant authorities in accordance with the Human Research Act (Art. 15) and HRO Art. 20.

Public and patient involvement

The selection of assessment tools and data collection instruments was guided by current scientific evidence on PCC and designed to reflect the broad spectrum of symptoms reported by patients worldwide. In addition, experiences and feedback from patients treated at the PCC clinic of the UHB were actively considered during the planning and development of the study protocol. Their input helped ensure the relevance and acceptability of the assessment procedures used in this study.

Guidelines

The development of this study protocol was informed by the Standardised Protocol Items Recommendations for Observational Studies checklist.[48] For future publications of study results, we will follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[49] to ensure transparent and comprehensive reporting.

Open science

There are currently no plans to make participant-level data publicly available. However, individual and aggregated study data will be shared with consortium partners in accordance with a joint controllership agreement that ensures compliance with applicable data protection regulations.

A copy of the informed consent form can be provided on request. Statistical code used for data analysis will also be made available on request once the analyses have been completed.

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