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Project Title

The Post-Covid-19 Syndrome: network building and innovative management to address a new public health emergency *(La sindrome post-Covid: far fronte ad una nuova emergenza di sanità pubblica con una gestione innovativa e il network building)*

Principal Investigator

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Executive Summary

Summarize aims, strategy and expected results.
(maximum 5000 characters) – 4,343 characters

The post-acute Covid Syndrome (PASC) is an emergent chronicity which has the potential to heavily impact not only individual health, but also local communities. Its features and burden are not well defined, nor are the models and protocols for its care by Health Care Systems. These challenges require a multidisciplinary approach, in order to define PASC in magnitude and describe it in features. A plan for systematic, structured intervention must be devised and implemented. This plurality of tasks requires the involvement of different institutions, with the construction of a network to deal with such a demanding work.

The overarching aim of the present project is to develop a solid network linking local health providers (ASSTs), a Scientific Institute for Research, Hospitalization and Health care (IRCCS), central health institutions (ATSs), General Practitioners and Universities to fill the current gap of knowledge on PASC from an epidemiological, clinical, and public health perspective. This multidisciplinary approach will be crucial for the design of effective intervention plans for the monitoring and management of PASC. The project will also explore the impact of the pandemic on contraction and changes in the provision of health-care services (namely outpatient services and screening tests) and disrupted care management of fragile patients, to locate priorities of intervention, particularly for the continued care of persons with chronicity and/or fragility.

In order to investigate the main features of the PASC, the project will first perform an epidemiological study on administrative health data regarding Covid-19 patients, from the beginning of the epidemic on, to characterize patients in terms of severity of the disease, path of care and PASC characteristics. Based on the epidemiological study, it will design and develop a clinical follow-up study on Covid-19 patients to determine the real incidence of PASC, its known and possibly yet-unknown manifestations in the population residing in the territories of the partner ASSTs and IRCCS. A GDPR-compliant digital infrastructure, available to all ATSs, will be created to show to the clinicians of each ASST and IRCCS the list of patients to follow-up and the visit or exams they need to perform. The same platform will allow the clinicians to visualize patients' information from administrative databases concerning the primary infection, previous hospitalization for Covid-19, comorbidities and vaccination status. The platform will allow to collect the results of the examinations planned during the follow-up and the data of interest from previous clinical records.
The epidemiological and clinical data from the first two studies will be integrated with clinical databases on Covid-19 patients already existing in the partner ASSTs and IRCCS. Such integration would serve not only for the objectives of the present project, but it will also be the basis for a prospective, observational, long-period cohort study which will follow Covid-19 patients in their various outcomes of disease. The so acquired information will be used to develop plans for the monitoring and management of the new PASC-related chronicity, both at patient- and system-level, with a strong focus on organizational models and digital health solutions, which can support the network and monitoring activities. The feasibility and efficacy of such intervention plans will be then evaluated and validated together with GP cooperatives included in the network. Finally, administrative health data will be used to evaluate the indirect effects of the epidemic on the Health-Care System, in terms of contraction and changes in health services (outpatient services and screening) and the short-term effects on emergency care access and emergency hospitalization due to a decrease in preventive services.

The main novelty of the project stands in its thoroughly exploration of the public health and social implications of PASC, through a combination of epidemiological, clinical, health-managerial, and economic methods. We expect, from the integration of all the competences of the various components of the network, to develop a clinically sound model, adequately dimensioned on epidemiological data, economically sustainable and easily implementable trough health management innovations.

Background and project rationale

Explore the existing knowledge and background literature on Post Acute Sars-Cov2 Syndrome. Describe the clinical and social welfare needs. Identify the gap[s] the project intends to fill in terms of effective collaboration between health care organizations. Specify in which way[s] this project represents a significant step forward.

(maximum 20.000 characters) – 9,244 *characters*

Post-acute Covid Syndrome, or PASC (Post-Acute Sequelae of Covid-19), is defined as a set of signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by alternative diagnoses.
NICE guidelines identify four types of Covid-related syndromes, according to the length of clinical manifestations:[1]

- Acute Covid-19: signs and symptoms of Covid-19, lasting until 4 weeks;
- Ongoing symptomatic Covid-19: signs and symptoms of Covid-19 lasting 4 to 12 weeks;
- Post-Covid-19 syndrome: signs and symptoms of Covid-19 lasting more than 12 weeks and not explained by an alternative diagnosis;
- Long Covid: signs and symptoms which appear or persist after an acute infection by Sars-Cov-2. It includes ongoing symptomatic Covid-19 and post-Covid-19 syndrome (signs and symptoms lasting over 4 weeks).

This project will deal with the post-Covid-19 syndrome (> 12 weeks of signs and symptoms). The list of persisting symptoms reported by patients is extensive: dyspnea, cough, anosmia, ageusia, asthenia, and neuropsychiatric symptoms.[2,3] Several studies, based on administrative health data on hospital admissions and risk of re-admission, have shown that patients discharged following a Covid-19 hospitalization present an increased risk of suffering again from respiratory diseases, and of incurring in cardiovascular, hepatic, renal diseases, and diabetes.[4] Studies dealing with Covid-19 patients follow-up showed analogous results. An US multicentric observational cohort study, evaluating 1,250 Covid-19 patients at 60-days from discharge, found that one-third of patients who completed a telephone survey reported persistent symptoms, of which about 20% with new or worsened ones.[5] The most common symptom was dyspnea while walking up the stairs (23%), and other symptoms included cough (15%) and persistent ageusia/anosmia (13%). Similar findings were reported from studies in Europe. A French study on 150 non-critical Covid-19 survivors described symptoms persistence in around 65% of individuals at 60 days, with 30% declaring to feel worse than at diagnosis.[6] Symptoms persistence was reported in about 90% of patients that had been hospitalized after 60 days from symptoms onset in an Italian post-acute outpatient service report.[7] The most commonly reported symptoms were fatigue in more than half of the patients, followed by dyspnea, joint and chest pain. Half of the patients were experiencing three or more symptoms and 44% of patients reported a decline in quality of life. Other studies, including follow-up studies at 8–12 weeks after hospital admission of 110 Covid-19 patients in the United Kingdom[8] and 277 survivors in Spain at 10–14 weeks after onset,[9] as well as 183 survivors in the United States at 35 days,[10] survey studies of 100 patients in the United Kingdom at 4–8 weeks post-discharge,[11] and 120 patients discharged from hospital in France, at 100 days following admission,[12] reported similar findings. In these studies, approximately 30% or more participants at the time of follow-up reported fatigue, dyspnea and neuropsychiatric symptoms, such as post-traumatic stress disorder (PTSD), depression, anxiety and sleep and concentration abnormalities. Factors associated with the presence or persistence of symptoms, pulmonary function/radiographic abnormalities, and reduction in health-related quality of life scores are admission to an intensive care unit and/or requirement for non-invasive/invasive mechanical ventilation.[8,11,13]
Sex differences also seem to matter, with women more likely to experience anxiety/depression and fatigue at 6 months follow-up, similar to SARS survivors.[13] While other comorbidities (e.g. diabetes, obesity, chronic cardiovascular or kidney disease, cancer and organ transplantation) are established determinants of increased severity and mortality related to acute Covid-19,[14,15] their association with post-acute Covid-19 outcomes in those who have recovered remains to be determined.

Clinical data about PASC among children are limited. A 2020 Swedish case report with systematic review first suggested that PASC in children may be similar to adults: persistent symptoms and signs included dyspnea, fatigue, heart palpitations/chest pain, headaches, difficulty concentrating, muscle weakness, dizziness, and sore throat at 6 to 8 months after primary infection; a case of myopericarditis was described

in the study.[16] A follow-up letter in early 2021 depicted the follow-up of 35 Swedish children with long-term symptoms similar to the initial report.[17] An Italian cross-sectional study observed 129 children diagnosed with Covid-19: when assessed 120 days after diagnosis 29 of those completing follow-up (42%) were still distressed with symptoms, including insomnia, respiratory symptoms (chest tightness and pain), fatigue, nasal congestion, muscle and joint pain, and concentration difficulties. Three children developed Multisystem Inflammatory Syndrome (2%) and two had myocarditis (1.6%).[18] A Latvian cohort study on 236 pediatric Covid-19 patients with a median follow-up time from acute symptom onset of 73.5 days found that at the time of interview almost three-quarters of children reported at least one persistent symptom, with the majority of patients (53%) having two or more concurrent symptoms.[19]

The post-Covid-19 syndrome appears sizeable in magnitude, with around one case of PASC every 10 Covid patients estimated for UK in November 2020[20] and younger women seem to be more exposed, with a doubled chance of suffering from PASC.[9,21] However, evidence on the clinical characteristics of the syndrome, its prevalence, risk factors or differential incidence and features among vaccinated and unvaccinated patients is still limited.
The overarching aim of the present project is to develop a solid network linking local health providers (ASSTs), a Scientific Institute for Research, Hospitalization and Health care (IRCCS), central health institutions (ATSs), General Practitioners and Universities to fill the gap of knowledge on PASC, from an epidemiological, clinical and public health perspective, which will be crucial for the design of effective intervention plans for its monitoring and management. As PASC is now established as a new emerging chronicity, a joint effort is in fact needed by the soon-to-be constituted local health providers, like the "Case della Comunità", "Ospedali di Comunità", "Centrali Operative Territoriali" (Districts of the ASSTs), and their dedicated health professionals (community and family nurses) in tight connection with hospitals (Departments of ASSTs) and primary care physicians, supported and coordinated by the Agencies for Health Protection (ATSs). The present project intends to provide a rationale, based on increased scientific knowledge on PASC and on the estimation of the actual prevalence of its different manifestations, to build an organizational model which will include all the aforementioned actors in the monitoring and management of PASC patients. This is crucial to meet the actual needs of the studied population, shaping supply and organizational aspects of the local health system on its actual demand.

Secondarily, the project will explore the impact of the pandemic on contraction and changes in the provision of health-care services (namely outpatient services and screening tests) and disrupted care management of fragile patients, to locate priorities of intervention, particularly for the continued care of persons with chronicity and/or frailty. As a matter of fact, still little is known about the indirect effects of the epidemic, in terms of reduction and modification of health-care provision, and in terms of obstacles to the fruition of outpatient services and screening. Some preliminary studies show a reduction in the utilization of health-care services not only for routine services, but for emergency care as well, and for chronicity.[22] Nevertheless, some studies suggest the existence of a rebound effect in the provision of outpatient services, meaning the tendency to return to pre-pandemic volumes of supplied medical care.[23] Data on missed oncologic diagnoses is of particular concern: the Italian National Observatory on Screening, by comparing the first nine months of 2019 and the first nine months of 2020, estimated a reduction of over one million calls for cervical screening (-40%), almost a million calls for mammography (-34%), and almost two million calls for colorectal cancer screening (-42%).[24] A February 2021 OECD report showed how the reduction in the utilization of health services has been driven not only by organizational factors related to the emergency (supply side), but also by personal motivation, like the reluctance to visit hospitals during the pandemic (demand side).[25] For this reason, it is the intention of National Health System to experiment in local providers for health promotion, prevention, care and rehabilitation of various categories of fragile patients. The success of such experiment crucially depends on the definition of the epidemiological features of the population of interest, and on the construction of proper indicators, related to real health needs.

Relevance to the call

Provide information about project's aims and expected results exploring how these fit in with objectives and strategy as stated in the Call.

(maximum 10,000 characters) - 6,746 characters

In accordance with the key priorities set in the current Call for Proposal, the project focuses on the epidemiological, clinical and social aspects of the post-Covid-19 syndrome, with the aim of developing intervention plans to effectively respond to this newly emerged chronicity and associated health-care needs.

In particular, the project aims at creating a network across central health institutions (ATSs), local health providers (ASSTs), a Scientific Institute for Research, Hospitalization and Healthcare (IRCCS), General Practitioners and Universities, that will:

- perform an epidemiological study on administrative health data regarding Covid-19 patients, from the beginning of the epidemic on, to characterize patients in terms of severity of the disease, path of care and characteristics of the PASC;
- exploit such epidemiological evidence to design and develop a clinical follow-up study on Covid-19 patients to determine the real incidence of PASC, of its known and possibly yet unknown manifestations in the population residing in the territories of the partner ASSTs and IRCCS;
- integrate epidemiological and clinical data from these studies, with clinical databases on COVID-19 patients already existing in the partner ASSTs and IRCCS. Such integration would serve for the objectives of the present project but would also be the basis for a prospective, observational, long-period cohort study which will follow Covid-19 patients in their various outcomes of disease;
- use all the acquired information to develop plans for the monitoring and management of the new PASC-related chronicity, both at patient- and system-level, with a strong focus on organizational models and digital health solutions, which can support the network and monitoring activities. The feasibility and efficacy of such intervention plans will be then evaluated and validated together with GP cooperatives included in the network;
- use administrative health data to evaluate the indirect effects of the epidemic on the Health-Care System, in terms of contraction and changes in health services (outpatient services and screening) and the short-term effects on emergency care access and emergency hospitalization due to a decrease in preventive services.

The network will be realized through the creation of a shared information system, which will integrate the collected epidemiological data of the population, administrative health data covering periods before, during and after the pandemic, and clinical information retrospectively (through consultation of medical records) and prospectively collected.

The involvement of several partners and stakeholders in the activities planned will allow for fruitful interactions in the definition of objectives and methods, as well as in the dissemination of the main findings and the implementations of the actions and policy initiatives at the local level.

Within this project, we expect to accomplish noteworthy results:
- a crucially needed gain in knowledge of PASC, in its epidemiological, clinical and social features;
- the establishment of an efficient and integrated system of follow-up, based on the actual health needs of the population;
- a plan for the catching-up with the missed and overdue screening services, and for the recovery of the disrupted services for chronicity care.

The pandemic is spurring a profound transformation for health-care strategies and structures, at both organizational and ecosystem levels. Besides clinical interventions, this scenario is assigning more and more relevance to managerial aspects and models for innovation implementation, with special attention to the rethinking of care pathways. In such a context, the new PASC-related chronicity plays a central role, for its implication on how healthcare is organized across spaces and territories, and on society as a whole. Indeed, PASC stretches the effect of the disease across space and time, affecting how healthcare systems are reorganizing themselves over territories and along the entire patient journey. It pushes - upstream - the rethinking of principles and processes for prevention and diagnosis, and - downstream - an expansion of goals, scope, and timelapse for follow-up activities.
The COVID epidemic has in fact highlighted that, when territorial health services are too fragmented, they are not able to respond adequately. During the epidemic phases, as well as in the surveillance phases, new organizational models have emerged, really ‘taking charge’ of the COVID patient. The experience of the pandemic has also highlighted:
-the importance of being able to adequately exploit the most advanced technologies
-the need to develop higher digital, professional, and managerial skills for health workers
-the necessity to establish new processes for the provision of services and care and
-the urge for a more effective connection between research, epidemiological data analysis, and delivered care and their programming at the system level. The goal is to build a common language for the overall evaluation, which contains not only the individual care plan but also the health path and prevention activities. In the new integration models pictured in the Piano Nazionale di Ripresa e Resilienza (PNRR), the strengthening of proximity networks, structures and telemedicine systems for territorial health care is

considered central. The PNRR strategy includes multidimensional interventions for improvements in chronic disease care, including the combination of multi-pronged strategies as a model for the treatment also of emerging pathologies. In the ATS of Milan, organizational models have been developed in some ASST based on the integration between hospital specialists, general practitioners, with the use of telemedicine tools for surveillance and the construction of multidimensional assessment techniques, also shared with the Municipalities and other socio-sanitary actors in the area.[26] With this project, the new and more articulated models of management developed for acute Covid will be now translated and adapted to the new chronic condition represented by the long-term effects of Covid-19, characterized by a combination of pathologies with differences between children, adults and the elderly. As PASC is now established as a new emerging chronicity, a joint effort is in fact needed by the the soon-to-be constituted local health providers, like the "Case della Comunità", "Ospedali di Comunità", "Centrali Operative Territoriali" (Districts of the ASSTs), and their dedicated health professionals (community and family nurses) in tight connection with hospitals (Departments of ASSTs) and primary care physicians, supported and coordinated by the Agencies for Health Protection (ATSs).

Experimental plan

Describe: i) actions planned and methods; ii) expected outputs; iii) milestones and deliverables; iv) monitoring and assessment indicators; v) a tentative timetable (Gantt); vi) consider potential pitfalls and caveats, discussing possible difficulties and limitations.

(maximum 25.000 characters excluding figures, tables and pictures) – 23,644 characters

WP-1 Retrospective epidemiological study

Organizational structure of WP1 is shown in Table 1

Table 1: organizational structure of WP1

	Lead	Coordinator	Partners/Supporting Stakeholders involved
WP1	ATS Milano	Antonio Giampiero Russo	ATS Bergamo, ATS Brescia, ATS Brianza, ATS Montagna, ATS Pavia, ATS Valpadana, UCSC

OBJECTIVES:
WP1 will delineate the population impact of PASC using administrative health data, clarifying the role of severity of the clinical manifestations, type of assistance received, infection/reinfection and previous vaccination on PASC.

TASKS:
- T1.1 – Cohort selection: The seven partner ATSs will conduct an epidemiological study, including all patients with a Covid-19 diagnosis (positive PCR nasopharyngeal swab test) in the period 1 March 2020-31 March 2021, residing in their territories (about 800,000 cases). To investigate Coronavirus sequelae in asymptomatic Covid-19 patients, also cases with a serologic test confirming previous infection in an unvaccinated person will be included.
- T1.2 – Health data collection and stratification: for each case we will recover the medical history, using administrative health data available to ATSs. Analyses will be stratified by severity of infection, type of assistance (treated at home, hospitalized in acute wards/ICU), and infection/reinfection. This last stratum will allow to investigate if a second Covid-19 infection in previously recovered individuals can cause different sequelae. We will develop specific algorithms in order to identify from administrative health data, like emergency department visits and hospitalizations, specific outcomes of interest, such as acute cardiovascular events, thromboembolisms, and respiratory emergencies. We will also evaluate patients' vital status and cause of death through the mortality registers of the ATSs, and the issuing of co-payment exemptions for PASC-related illnesses starting 12 weeks or later after the acute infection. We will also consider repeated outpatient services utilization for pneumological, cardiologic, neurologic or psychiatric visits and develop an algorithm specific for pediatric patients. With the same methodology, we also plan to evaluate possible differences in PASC between vaccinated and unvaccinated patients, by analyzing all cases of Covid-19 between 1 January 2021 and 31 March 2022 in people fully vaccinated, and separately for those infected after the third dose, stratifying for type of vaccine received. We will extract data for the period preceding Covid-19 infection from administrative health data, to describe already present comorbidities

and the consumption of certain drug categories (e.g. antidepressant, bronchodilators) for pre-post comparison. Table 2 shows the distribution of cases across ATSs.

Table 2: distribution across the network ATSs of the cases included in the epidemiological study

ATS of residence	Frequency	Percentage	Cumulative freq.
ATS Bergamo	63973	8,3%	63973
ATS Brescia	124553	16,1%	188526
ATS Brianza	115715	15,0%	304241
ATS Milano	333618	43,1%	637859
ATS Montagna	16799	2,2%	654658
ATS Pavia	47900	6,2%	702558
ATS Valpadana	70975	9,2%	773533

- T1.3 – Sampling for clinical follow-up: to perform the tasks of WP2, we will select samples of the cohort defined in T1.2 residing in each Partner ASST and distribute them to ASSTs to perform clinical follow-up (WP2). We will extract a representative case sample, performing a stratified randomization by gender, age class, acute-phase manifestation (asymptomatic, symptomatic by symptom type/aggregation) and by infection/reinfection. To evaluate the sample size needed to detect the existence of each PASC abnormality, we executed a review of existing literature regarding their prevalence in the convalescent Covid-19 population. We performed a sample size calculation[27] using the formula

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where n is the sample size, Z the value from the standard normal distribution reflecting the confidence level that will be used, P the expected prevalence of the symptom or sign derived from literature, d is precision. We chose a level of confidence of 95%, and we selected d according to the value of P, with the conservative value $d = P * 0.2$. Table 3 shows the estimated sample sizes.

Table 3: estimated sample sizes

Finding	Test	Hospitalized patients	
		Estimated finding prevalence	Sample size
Anomalous pulmonary volumes	spirometry	0,42	133
Anomalous pulmonary imaging	chest CAT	0,5	96
Anomalous DLCO	DLCO	0,22	341
Myocardium inflammation	heart MR	0,15	544
Left systolic dysfunction	heart US	0,31	214
Hematological abnormalities	blood panel	0,13	643
Neurologic/Psychiatric alterations	neurologic/psychiatric examination	0,4	144

It is difficult to estimate the prevalence of abnormalities in patients who underwent a mild form of the disease, since scant evidence is available in the literature regarding mild and asymptomatic infections, and most of it regards clinical, self-reported symptoms. Few studies investigated the prevalence of pathologic findings through imaging or other instrumental tests in this subset of patients. Conversely, the needed sample size can be calculated for previously hospitalized patients, for which prevalence estimations are available in literature. Regarding neurologic and psychiatric examinations, we will select the sample of 144 patients to refer to either of the disciplines through a first-level screening process performed during pneumological, cardiological or GP examination, utilizing validated simplified tests and selecting patients that more likely need a specialist assessment. Hematologic abnormalities can refer to either inflammation markers or signs of decreased renal function. Available literature on the inflammation markers analyzes differences in markers' levels between individuals with or without previous Covid-19 infection, but does not deal with the prevalence of findings over normal threshold. Conversely, prevalence of decreased renal function as compared to the period preceding infection has been described. For all blood tests, the sample

size has thus been calculated utilizing the prevalence of increased creatinine with respect to the pre-infection period (13%).[13] Regarding the clinical examinations, the sample size has been calculated estimating a prevalence equal to the lower prevalence among those estimated for the tests which require the presence of the specialist (e.g. for pneumological examination: specialist required for spirometry and for DLCO; estimated prevalence of anomalous spirometry in the population = 42%, estimated prevalence for anomalous DLCO = 22%; estimated prevalence for pneumological examination = 22%). For GP examination we calculated a sample size able to detect anomalous findings with an estimated prevalence of 8%, resulting in 1825 patients. We will distribute the sample between the partner ASSTs proportionally to the number of Covid-19 cases registered among the residents in their territory. We will also extract a sample of pediatric patients. The sample size will be redetermined after preliminary exploration of administrative data, given the lack of reliable prevalence estimates. Tables 4 and 5 depict the distribution of cases across network ASSTs/IRCCS and the prospected sample division, respectively.

Table 4: distribution of Covid-19 cases across partner ASSTs

Partner ASST	Cases	Perc.	Cumulative cases
ASST DI CREMA	12295	6,4%	12295
ASST DELLA FRANCIACORTA	22596	11,7%	34891
ASST DEL GARDA	37085	19,2%	71976
ASST DI LODI	19833	10,3%	91809
ASST OVEST MILANESE	43076	22,3%	134885
ASST DI PAVIA/IRCCS SAN MATTEO	47290	24,5%	182175
ASST DELLA VALCAMONICA	10710	5,6%	192885

*Table 5: allocation of tests across partner ASSTs**

Test	Total sample size	ASST DI CREMA	ASST DELLA FRANCIA-CORTA	ASST DEL GARDA	ASST DI LODI	ASST OVEST MILANESE	ASST DI PAVIA IRCCS SAN MATTEO	ASST DELLA VALCA-MONICA
Pneumologic ex.	**341**	22	40	65	35	76	83	19
Chest CAT	**96**	6	11	18	10	21	24	5
Spirometry	**133**	8	16	25	14	30	33	7
DLCO	**341**	22	40	65	35	76	83	19
Cardiologic ex.	**214**	14	25	41	22	48	52	12
Heart ultrasonography	**214**	14	25	41	22	48	52	12
Cardiac MR	**544**	35	64	105	56	122	133	30
Neurologic/Psychiatric ex.	**144**	9	17	28	15	32	35	8
Blood tests	**643**	41	75	124	66	144	158	36
GP examination	**1104**	70	129	212	114	247	271	61

**the distribution has been calculated as the total number of specific tests for the diagnostic category multiplied for the proportion of cases in that ASST over the total cases of all partner ASSTs*

Table 6 shows milestones and deliverables for WP1

Table 6: milestones and deliverables for WP1

Milestone	Description	Estimated period (project months)
M1.1	Identification of the cohort of Covid-19 subjects and sampling for WP2	1-3
M1.2	Development of algorithms to detect PASC events from administrative data	4-10
M1.3	Results of epidemiologic analysis to detect determinants of PASC	8-13
Deliverable	**Description**	
D1.1	List of Covid-19 patients to be followed for PASC detection	
D1.2	Research report on data analysis and policy implications	
D1.3	WP and publication on peer reviewed international journals	
D1.4	Presentation, workshop and other dissemination activities both to academic and non-academic audiences.	

WP-2 Prospective clinical study

Organizational structure of WP2 is shown in Table 7

Table 7: organizational structure of WP2

	Lead	Coordinator	Partners/Supporting Stakeholders involved
WP2	Steering committee of ASSTs, IRCCS and GPs representatives	President of the steering committee	ASST Crema, ASST Franciacorta, ASST Garda, ASST Lodi, ASST Milano Ovest, ASST Pavia, ASST Valcamonica, IRCCS Policlinico San Matteo, ATS Bergamo, ATS Brescia, ATS Brianza, ATS Milano, ATS Montagna, ATS Pavia, ATS Valpadana, UCSC

OBJECTIVES:
WP2 will delineate the clinical impact of PASC through a follow-up of Covid-19 patients. Subjects will be examined by GPs or by specialists, clarifying the role of infection seriousness, type of assistance received, infection/reinfection and previous vaccination on PASC.

TASKS:
- T2.1 – Development of protocols for specialists and GPs: the evaluation of different aspects of PASC will be performed by the network ASSTs and IRCCS, according to their specializations and clinical interests. The ASSTs and IRCCS will cooperatively develop specific protocols for the identification, monitoring and control of the neurological, cardiological, pneumological or psychiatric sequelae of Covid-19. The associations of GPs included in the network will be involved in the definition of the protocol and will perform clinical examinations and questionnaires administration of patients treated at home. Previously hospitalized patients will be referred to hospitals to undergo more complex tests. A dedicated protocol will be developed for mountainous areas, favoring tele-monitoring. ASSTs with specific specialist competences could be dedicated to more intense screening for a specific clinical area. The issue of post Covid-19 rehabilitation will also be investigated. Based on literature evidence regarding Covid-19 and infections from other coronaviruses, we can anticipate that the following tests and procedures could be included in the protocols:
GPs: pulse oximetry, peak expiratory flux, blood pressure measurement, clinical questionnaire administration;[28]
all areas: pulse oximetry, blood pressure measurement, clinical questionnaire administration, chest CAT, blood panel for evaluation of organ damage and inflammatory state (creatinine, CRP, IL-6, NT-proBNP, ferritin, D-dimer);[2,13,29-33]
pneumology: test of lung function through spirometry and DLCO;[2,34-38]
neurology/psychiatry: evaluation of cognitive impairment, anxiety and depression through validated scales;[2,39-42]
cardiology: transthoracic echocardiography, cardiac MR.[2,43-47]
Components of the network possessing particular technological resources can investigate certain features of the disease in greater depth, principally through advanced laboratory examinations.
- T2.2 – Infrastructure for data collection: ATSs Valpadana will develop a GDPR-compliant digital infrastructure, available to all ATSs, to show to the clinicians of each ASST and IRCCS the list of patients to

follow-up and the visit or exams they need to perform. The same platform will allow the clinicians to visualize patients' information from administrative databases concerning the primary infection, previous hospitalization for Covid-19, comorbidities and vaccination status. The platform will allow to collect the results of the examinations planned during the follow-up and the data of interest from previous clinical records. A data manager, shared between the ATSs, will have data quality control and data abstraction functions.

- T2.3 – Patients' follow-up and extraction of previous health status from clinical records: utilizing the samples extracted in WP1, each network ASST and IRCCS will perform the follow-up of the sampled patients residing in its territory. All included cases will undergo the tests and examination agreed in T2.1 for the specific types of patients and settings. The medical records of all the sampled patients which were hospitalized as a consequence of the acute infection will be reviewed during the follow-up, to extract the information on the primary infection symptoms and severity, blood test and functional parameters. This information will be compared with data collected during follow-up in order to evaluate changes over time. We will then perform sub-sample analyses to identify potential differences between genders or age classes. We also plan to evaluate Covid-19 sequelae in infections following vaccination in hospitalized patients: we will analyze the sequelae of a subsample of cases of Covid-19 between 1 January 2021 and 31 March 2022 in fully vaccinated patients, and separately for patients who received a third dose. Each case will be treated with the methodology stated above, stratifying for type of vaccine received, in order to ascertain possible differences in PASC between vaccinated and unvaccinated patients.
- T2.4 - Validation of the algorithms to detect PASC from administrative health databases: the algorithms to detect the presence of PASC and its specific manifestations (e.g., acute cardiovascular events, thromboembolisms, respiratory emergencies) from administrative databases (T1.2) will be validated against the data collected during the clinical follow-up study. We will calculate for every algorithm, corresponding to a clinical event, and for PASC as a whole, the sensibility, sensitivity and predictive values.

Table 8 shows milestones and deliverables for WP2.

Table 8: milestones and deliverables for WP2

Milestone	Description	Estimated period (project months)
M2.1	Definition of clinical follow-up protocols	1-4
M2.2	Execution of clinical follow-up of the sampled patients	5-12
Deliverable	**Description**	
D2.1	Standardized clinical follow-up protocols	

WP-3 Model for a long-term, prospective cohort study for Covid-19 patients

Organizational structure of WP3 is shown in Table 9

Table 9: organizational structure of WP3

Lead	Coordinator	Partners/Supporting Stakeholders involved
UNIMIB	Maria Grazia Valsecchi	ASST Crema, ASST Franciacorta, ASST Garda, ASST Lodi, ASST Milano Ovest, ASST Pavia, ASST Valcamonica, IRCCS Policlinico San Matteo, ATS Bergamo, ATS Brescia, ATS Brianza, ATS Milano, ATS Montagna, ATS Pavia, ATS Valpadana

OBJECTIVES:
WP-3 intends to create a model to perform long-term follow-up of COVID-19 patients by means of

- defining a model for the integration of administrative data and clinical data from this project and the clinical databases (with biological samples, if available) on COVID-19 patients already existing in the Partner and collaborating ASSTs;
- to develop a sound methodology for the long-term outcome data analysis.

TASKS:

- T3.1 Estimation of the prevalence of PASC symptoms. The data from the clinical follow-up study (T2.2), linked with the administrative data (T1.2), will be used to estimate the prevalence of the different symptoms of PASC, overall and in the defined subgroups (pediatric patients, vaccinated vs. non-vaccinated, hospitalized in ICU vs. hospitalized non-ICU vs. never hospitalized patients, patients with previous respiratory, cardiovascular and metabolic comorbidities). Also, data will be analyzed i) to detect the presence or the combination of not previously reported findings and ii) to differentiate hospitalized patients according to length of stay, including sub-acute and Covid-19 ward transfers.
- T3.2 - Definition of a model to integrate administrative and clinical data: we will develop a model to integrate administrative data from the ATS, concerning infection, vaccination status, hospitalization and PASC syndrome events and clinical databases collecting data (and samples) at hospitalization of Covid-19 patients already existing in some ASSTs (study partners or supportive stakeholders). The integration will allow to model PASC occurrence and outcome with the inclusion of additional clinical details collected at hospitalization, thus on more severe cases, in the ASSTs, and may generate aetiological hypothesis to be tested in biological samples collected at hospitalization. The integration approach will be developed as a case-study on one of the clinical databases with a potential for generalizability on all clinical databases.
- T3.3 – Outcome analysis: occurrence of morbidities and mortality will be analysed with survival and event-history methodology and related to subject characteristics as collected in administrative as well as clinical data bases (in the case-study of T3.2). In addition, a comparison of event-history data in patients enrolled or not in the PASC follow-up will be performed, accounting for the complex sampling design and refusal to be enrolled in the clinical follow-up. For this reason, in the sampling of WP1, a "control" sample will be extracted with the same stratification criteria and not included in the clinical follow-up study. The morbidity and survival outcomes assessed in those with a clinical follow-up will be compared to the outcome in those not included (cohort of controls), based on health administrative data only. The comparison, performed at 6 months from the beginning of the follow-up program will allow to assess the effect of the clinical follow-up and related intervention. In addition, based on the outcome analysis, the frequency, severity, and timing of PASC following complete vaccination and dose booster will allow evaluating whether Covid-19 vaccination changed the severity and the timing of Covid-19 infection. Based on this, we will explore the possibility to simulate different scenarios aimed to assess how different policies of vaccination coverage with tailored strategies based on risk stratification models could affect the occurrence and frequency of PASC. We will consider the use of compartmental mathematical modelling methods that evaluate the transition of cases from susceptible, exposed, infected, and recovered to implement these simulations.

Table 10 shows milestones and deliverables for WP3.

Table 10: milestones and deliverables for WP3

Milestone	Description	Estimated period (project months)
M3.1	Definition of the integration model	4-8
M3.2	Estimation of prevalence of the different symptoms	10-14
M3.3	Analysis of morbidity and survival outcomes of patients in the case study (administrative and clinical data) and of sampled patients not included vs. included in the follow-up (administrative data only)	12-14
Deliverable	**Description**	
D3.1	Technical report on modalities of administrative and clinical data integration	
D3.2	Epidemiological report and publication on peer reviewed international journals of the estimated symptom prevalence and on the long-term outcome as related to patients characteristics and follow-up interventions	
D3.3	Presentation, workshop and other dissemination activities both to academic and non-academic audiences	

WP-4 Evaluation of the indirect effects of the epidemic on the Health System

Organizational structure of WP4 is shown in Table 11.

Table 11: organizational structure of WP4

	Lead	Coordinator	Partners/Supporting Stakeholders involved
WP4	UCSC	Claudio Lucifora	ATS Milano, ATS Bergamo, ATS Brescia, ATS Brianza, ATS Montagna, ATS Pavia, ATS Valpadana

OBJECTIVES:
WP4 will empirically evaluate the effects of the Covid-19 epidemic in terms of contraction and changes in the provision of health-care services (namely outpatient services and screening tests), as well as the short-term effects of such contraction on emergency care access and hospitalization, between 31 May 2018 and 31 May 2021. The empirical analysis will be carried out using high-frequency register data from network's ATSs on outpatient services and Covid-19 databases, with information on daily contagions, performed swabs, ICU admissions and Covid-19 deaths. In particular, the pre-and post-emergency effects will be investigated in terms of both organizational factors, such as bottle-necks and congestion (supply side), as well as behavioral effects, such as hesitancy to visit hospitals during the pandemic (demand side). Event study methodologies will be used in the empirical analysis.
In particular, WP4 will:

- Evaluate the impact of the Covid-19 epidemic on outpatient treatments and screening services;
- Assess the intensity of delayed medical care and explore congestion effects on health-care providers;
- Investigate the short-term effects of delayed or forgone critical preventive and diagnostic treatments on emergency care use and hospital admissions.
- Identify and profile different categories of fragile patients in need of prevention, care, and rehabilitation measures.

TASKS:

- T4.1 – Data cleaning and processing. Data cleaning, definition of the sample and variables of interest, data preparation;
- T4.2 – Analysis of impact of Covid-19 on the provision of health-care services. Exploit high-frequency data to compare daily trends of outpatient and screening services (mammographies, fecal occult blood tests, pap-tests) for specific monthly intervals before and after the hit of Covid-19. The issue of delayed medical care will also be evaluated in terms of intensity, measured as the number of months of activity that would be needed to fill the gap, should the provision of outpatients and screening tests proceed at the same pace with respect to the same months of the pre-epidemic years. Data on daily number of positive subjects, swabs, ICU admissions and deaths for Covid-19 (at the ZIP code level) will be used to analyze the congestion effect on health-care provides. Heterogeneous effects across category of diagnosis, age class and chronicity will also be explored;
- T4.3 – Analysis of the short-term effects of foregone preventive care on access to emergency care and hospital admissions for selected diagnostic categories, and identification of prevention, care and rehabilitation measures for selected categories of fragile patients.

Table 12 shows milestones and deliverables for WP4.

Table 12: milestones and deliverables for WP4

Milestone	Description	Estimated period (project months)
M4.1	Outline a thorough characterization of the trends in the provision of health-care services (outpatients and screening tests) throughout Covid-19 epidemic	4-10
M4.2	Evaluate the intensity of delayed medical care, also considering congestion effects on health-care providers	6-12
M4.3	Identify short-term effects on emergency care and hospital admissions	10-15
Deliverable	**Description**	
D4.1	Research report, working paper and publication on peer reviewed international journals	
D4.2	Presentation, workshop and other dissemination activities both to academic and non-academic audiences	

WP-5 Development of plans for PASC management

Organizational structure of WP5 is shown in Table 13.

Table 13: organizational structure of WP5

Lead	Coordinator	Partners/Supporting Stakeholders involved
UNIPV	Stefano Denicolai	ASST Crema, ASST Franciacorta, ASST Garda, ASST Lodi, ASST Milano Ovest, ASST Pavia, ASST Valcamonica, IRCCS Policlinico San Matteo, ATS Bergamo, ATS Brescia, ATS Brianza, ATS Milano, ATS Montagna, ATS Pavia, ATS Valpadana, UCSC

OBJECTIVES: to provide a better understanding of organizational implications in managing and monitoring PASC through a multidisciplinary approach, combining clinical, epidemiological and management standpoints. In such a context, digital health is accounted as a key enabler as well as a driver of change. First, technologies like artificial intelligence, sensors, mobile APPs and wearable devices play a central role for ex-ante preventing and ex-post managing effects of PASC. Besides health care, technology has an effect on society as a whole and on workplaces. Second, a better exploration and integration of digital datastreams - overcoming siloing issues and combining different sources, including both clinical, epidemiological and administrative data - is a key consideration to make a step forward in the field, towards a 'digital innovation strategy'.
Due to the prospected strengthening of local health services, WP5 also aims at developing innovative patterns of collaboration among the different agents of the whole health-care system, with a particular focus on novel solutions recently introduced by institutional bodies (e.g., PNRR), and on chronicity issues.
The methodology consists of a desk analysis on data and organizational materials provided by partners. Principles of 'experimental design' are taken into account.

TASKS:
- T5.1 – Review of existing literature: extensive review of both medical and management studies, conducted through the "systematic literature" method. Grey literature will also be considered, though in a separated section and accounting for differences compared to scientific papers.
- T5.2 – Data and information gathering
- T5.3 – Desk analysis on administrative data and organizational materials provided by partners (e.g., charts, previous report, procedure, partner websites, etc.) and analysis of information through 'Topic modeling' and text mining methods, for an in-depth understanding of materials and to capture latent insights. Outcomes will be evaluated by a multidisciplinary team.
- T5.4 – Dissemination and networking workshop. Findings will be shared with partners and stakeholders through a scientific report and a workshop, also aimed at stimulating networking among health-care agents.

Table 14 shows milestones and deliverables for WP5.

Table 14: milestones and deliverables for WP5

Milestone	Description	Estimated period (project months)
M5.1	Identification of key management issues over management and monitoring of PASC	4-6
M5.2	Definition and validation - through project review with partners and a panel of experts - of recommendations for follow-up protocols	6-12
M5.3	Definition of an innovative organizational model and transformation journey principles for management and monitoring of PASC	10-14
Deliverable	**Description**	
D5.1	Recommendations for models and plans aimed at managing and monitoring PASC, together with the GP cooperatives included in the network. Special attention goes to key factors of success in leading this health-care transformation	
D5.2	Report on "Fighting PASC through health-care innovation and digital transformation: guidance and recommendations"	
D5.3	Presentation, workshop and other dissemination activities both to academic and non-academic audiences	

Dissemination Plan

Lead	Coordinator	Partners/Supporting Stakeholders involved
UCSC	Communication and dissemination Manager	ATSs, UCSC, UNIMIB, UNIPV

The dissemination plan will be focused on promoting and facilitating the use of effective intervention plans for the monitoring and management of PASC. All partners of the Network along with supportive stakeholders will play an active role in the dissemination, exchange and communication activities of the project to transfer knowledge and the main findings. To this end, a multi-channel dissemination strategy has been established in order to maximize the impact of the dissemination activities, carefully adjusting the materials and tools to the specific needs, interests and involvement of the target audience. The dissemination plan is going to be flexible and regularly updated. The following dissemination tools and activities have been planned:

1. Website and general repository at the ATS, ASST, IRCCS and GP levels

A dedicated website will be implemented and hosted at the CRILDA-Università Cattolica Research Center, and linked to other partner institutions' websites. The website will serve as general repository for intermediate results, minutes of the scientific committee meetings and other project's deliverables. The website will provide constant updates and easy access to the scientific community, public health institutions, as well as other stakeholders through cross-links with institutions and territorial supportive stakeholders. In addition, we plan to create an infrastructure for data collection, at the Valpadana ATS which will serve as data-hub for clinical data (i.e. patients to follow-up and visits or exams they need).
A communication manager will be in charge of the design and development of the website, while a data manager will be responsible for data-hub.

2. Public events and distance-learning activities for GPs and specialists involved in PASC diagnostic

We plan to organize a number of thematic workshops aimed at specialists active in the diagnostic of PASC, as well as public event for GPs operating in the territory of the seven partner ATSs, in order to share plans for the monitoring and management of PASC-related chronicity. The workshops and other events are intended disseminate information on the designed protocol for PASC diagnostic and treatment. We also plan to promote activities of distance-learning for all GPs in the Lombardy region.

3. Video-training on PASC diagnostic and treatment
To reach the vast audience of specialists, GPs, nurses and other stakeholders involved in PASC management, we plan to create video-training on PASC diagnostic and treatment as self-learning tools.

4. Scientific workshops
The project's findings will be shared with partners and stakeholders in intermediate and in a final workshop. These evidence-based interventions will be organized with the involvement of the academic institutions to disseminate the scientific research outputs and stimulate networking among health-care agents.

5. Policy briefs
Policy briefs and short articles delivered through online medical journals (i.e. "Quotidiano sanità", "Doctor33", "DottNet", etc.)

Monitoring and assessment indicators

Table 15 depicts the indicators for each WP, with relevant time-thresholds.

*Table 15: monitoring and assessment indicators for each WP, with relevant time-thresholds**

WP	Indicator	Description	Thresholds	
			Value	Time
WP-1	I-M1.1	Proportion of ASSTs for which the cohort identification and sampling for WP2 has been completed. We plan the sampling phase to last roughly three months: I-M1.1 should be 0.25 at three weeks, 0.5 at six, 0.75 at nine.	0.25	week 3
			0.5	week 6
			0.75	week 9
WP-2	I-M2.1	Proportion of diagnostic categories for which a clinical follow-up protocol has been completed (GPs, pneumology, cardiology, neurology/psychiatry, and diagnostic procedures common to all areas). We plan the protocol devising phase to last roughly four months: I-M2.1 should be 0.5 at two months.	0.5	month 2
	I-M2.2A	Proportion of patients from the sample for which the execution of the clinical follow-up has started, measured for each ASST level according to the portion of the sample attributed. The entire follow-up phase should last 8 months; I-M2.2A should be 0.5 after 4 months, and 1 after 7 months from the start of the clinical follow-up phase.	0.5	month 4
			1	month 7
	I-M2.2B	Proportion of patients from the sample for which the execution of the clinical follow-up has been completed, measured for each ASST level according to the portion of the sample attributed. The entire follow-up phase should last 8 months; I-M2.2B should be 0.25 after 4 months, and 0.5 after 6 months from the start of the clinical follow-up phase.	0.25	month 4
			0.5	month 6
WP-3	I-M3.1	Advancement of M3.2 and M3.3 should run in parallel with the progress of the clinical study (WP2), since they rely on the analysis of its data. We plan to integrate in M3.2 and M3.3's analyses the information from enrolled and examined patients not later than a month from the communication of the data by the ASSTs/IRCCS.	1	one month from communication of the data
WP-4	I-M4.1 - I-M4.2	Advancement of M4.1 and M4.2 should run in parallel with WP5 concerning the reorganization of public health systems. The analysis of delayed medical care and congestion effects should be completed by month 12.	1	month 12
WP-5	I-M5.2	Advancement of M5.2 should run in parallel with the beginning of the clinical study (WP2), as the managerial and organizational evaluations of M5.2 should be integrated with the clinical follow-up protocols. The first organizational reccomandations will be developed within 4 months and will be then updated regurarly during the project, based on observation.	1	month 8

**time values are calculated from the start of the descripted phase of the project*

Potential pitfalls and solutions

An evaluation of potential risks and mitigation strategy is described in Table 16, along with actions to be taken to minimize their effects.

Table 16: potential risks and mitigation strategy

Description of risk	WPs involved	Probability	Impact	Mitigation strategy
Underestimation of the timing planned for the execution of WPs	all WPs	likely	moderate	PI and partners will monitor progress of work in accordance to the task defined in the experimental plan. If needed, a redistribution of tasks or alternative approaches will be considered to reach deadlines.
Slow entrollment of patients in the clinical trials	WP2	quite likely	low-moderate	Due to the large number of ASSTs participating, we do not envisage particular problems in the enrollment of patients in the clinical trial (see project timeline. In the event of slow enrollment, an additional sample will be added to match the target number of patients for the analysis to be successful.
Ethical and privacy concerns with data collection	WP1-2-3	not very likely	moderate	Clearance of the Ethical Committe will be sought immediately after the project approval by all partners. Any problem of ethical or privacy concerns with data collection will be dealt with, reorganizing activities according with the issues raised. The studies conducted in the context of the present project will be performed according to EU regulation 2016/679 and EU directive 2016/680 (GDPR).
Management and coordination of the network	all WPs	low	low-moderate	The strong link and the long-standing cooperation among partners (Health Agencies and Associations) should mitigate this concern. A project manager will guarantee the coordination of activities among partners, the exchange of information and sharing of data, as well as meeting the deadlines.
Organizational and cultural resistance against change	all WPs	likely	moderate-high	Adoption of and experimental and incremental approach, aimed at showing benefits in a "safe" environment and capturing feedback in real-time; high effort on internal communication activities.
Difficulties in the development of data infrastructure	WP2	not very likely	high	Assistance by specialized professionals from ATS Valpadana, and by an ad-hoc contract data manager

Timetable (GANTT)

Table 17 depicts the tentative timetable for the project.

Table 17: GANTT

Workpackage	Partner responsible	Task	Month													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
WP-1: Retrospective epidemiological study	ATSs	T1.1	■	■	■												
		T1.2				■	■	■	■	■	■	■	■	■	■		
		T1.3	■	■	■												
WP-2: Prospective clinical study	ASSTs	T2.1	■	■	■	■											
		T2.2	■	■	■	■											
		T2.3					■	■	■	■	■	■	■	■			
WP-3: Long-term, prospective cohort study for Covid-19 patients	UNIMIB	T3.1										■	■	■	■	■	
		T3.2				■	■	■	■	■							
		T3.3												■	■	■	
WP-4: Evaluation of the indirect effects of the epidemic on the Health System	UCSC	T4.1	■	■	■	■	■	■									
		T4.2							■	■	■	■	■	■			
		T4.3										■	■	■	■	■	■
WP-5: Development of plans for PASC management	UNIPV	T5.1	■	■													
		T5.2		■	■	■	■	■									
		T5.3					■	■	■	■	■	■	■	■	■	■	
		T5.4															■

Project originality and innovation

Indicate how the project introduce novel approaches or methods in care pathways.

(maximum 3000 characters) 2,779 characters

We believe this project to be both ambitious in scope and innovative in methods. To the best of our knowledge, PASC, its public health and social implications have not yet been explored thoroughly, especially through a combination of epidemiological, clinical, health-managerial, and economic methods. The integration of all the competences of the various components of the network will allow to develop a clinically sound model, adequately dimensioned on epidemiological data, economically sustainable and easily implementable trough health management innovations. The development of novel models, paths and plans for management and monitoring of the PASC-related chronicity is grounded on principles of precision medicine from an organizational perspective.[48] The project aims at further innovating in this field by investigating how digital health and artificial intelligence can enable improvements in the healthcare systems designed for preventing patients with high risk of PASC, clustering types of PASC and then optimizing care and patient journey around specific features of people (precision). The model will also allow to develop participatory form of healthcare, integrating data capabilities from different sources of agents (network-based view).

The development of an innovative new care pathway for PASC will be based on real needs through epidemiological evaluation and on-field clinician involvement, both GPs and specialists, designed with original managerial approach exploiting digital medicine possibilities also in smaller care providers, and with a focus on coordinating the activity of local health providers with that of hospitals, in the spirit to provide integrated multifaceted personalized interventions with a one-health approach, also along the lines of the PNRR. The clinical guidelines developed with this approach will be formalized and diffused through the network to the health professionals of the region with both digital and traditional formats, to improve the actual management of PASC at any level of care. Also, the original managerial and organizational aspects of the project will be discussed with the general directorates of the Partners, to establish dedicated integrated pathways, tailored also on the specific age group and geographic and population characteristic of each ASST, and improve the experience of care of PASC patients. Seven out of eight ATSs of the Lombardy region will participate into the project, together with 8 Partners ASSTs and 5 more ASSTs that have expressed their interest. We thus believe that the innovative developed model could be easily implemented also in other ASSTs and IRCCS, and not only in the partners of the present project and serve as a model for future integrated health policy initiatives.

Impact

Describe how the project would improve PASC Syndrome patients' pathways. Explain how the proposed solutions can be a blueprint for other pathologies or in other communities. Indicate the impact on health care professionals.

(maximum 15,000 characters) – 3,935 *characters*

The project will impact population health in several ways: i) through a crucially needed progress in the scientific knowledge of PASC, both on its epidemiology (in terms of quantification and risk factors) and on its clinical characteristics; ii) through the development of an efficient and integrated system of clinical follow-ups, based on the actual health needs of the population; through intervention plans for the catching up with the missed and overdue screening services, and for the recovery of the disrupted services for chronicity care.

The cooperative development of specific protocols for the identification, monitoring and control of Covid-19 sequelae by ASSTs, IRCCS and associations of GPs will guide the follow-up of patients through clinical examinations and questionnaires administration, with the aim of clarifying the role of infection severity, type of assistance received, infection/reinfection and vaccination, and ultimately improve PASC patients' pathways. Moreover, the established multidisciplinary network of epidemiological, clinical, health-managerial and research institutions will serve as a blueprint for future collaborations, in all cases where a public health challenge requires an integrated management able to delineate its features and possible solutions.

All professionals included in the network will greatly benefit from the interdisciplinary cooperation, through an exchange of expertise which can continue even after the project conclusion. The externalities of the project will also be relevant to all professionals which might benefit from the developed plans and recommendations, not only for the management of PASC, but possibly as a model for the care and management of other chronicities as well.

The main impacts, divided into scientific and public health impacts, are listed below.

SCIENTIFIC IMPACT

- Provide robust evidence on PASC through different data sources (clinical data, administrative data and experimental data from follow-up studies).

- Development of a data integration model that contributes to

o a more refined prediction of the infection outcome and PASC;

o the generation of etiological hypotheses worth testing in stored biological samples;

o the design of prospective, observational and cohort studies on the long-term follow-up of Covid-19 patients for different health outcomes, identified on the basis of the results of this project (already known or newly found).

- Provide a comprehensive analysis of organizational issues regarding management and monitoring of PASC, aimed at the definition and validation of recommendations for follow-up protocols.

- Provide an assessment of the impact of the Covid-19 pandemic on the provision of health-care services and on the short-term effects of disrupted care on emergency care access and hospitalizations.

PUBLIC HEALTH IMPACT

- Development of a vast multidisciplinary network across the various levels of the Health Care System – ATSs, ASSTs/IRCCS both in their local (Districts) and hospital (Departments) components, General Practitioners – and Universities, which will allow

o the dissemination of recent scientific evidence on PASC;

o the definition of specific protocols for the identification, monitoring and control of Covid-19 sequelae to guide clinical follow-ups of Covid-19 patients;

o a solid and efficient cooperation among key actors of the Health Care System to cope with future public health challenges.

- Rising awareness on the specific needs of Covid-19 patients.

- Development of recommendations for the design of intervention plans for the catching up with missed and overdue screening services, and for the recovery of the disrupted services for chronicity care.

- Design of an innovative organizational model and intervention plans for the management and monitoring of PASC by the National Health Care System, which can guarantee patients' care, treatment, and long-term follow-ups.

Partnership, governance and scientific committee

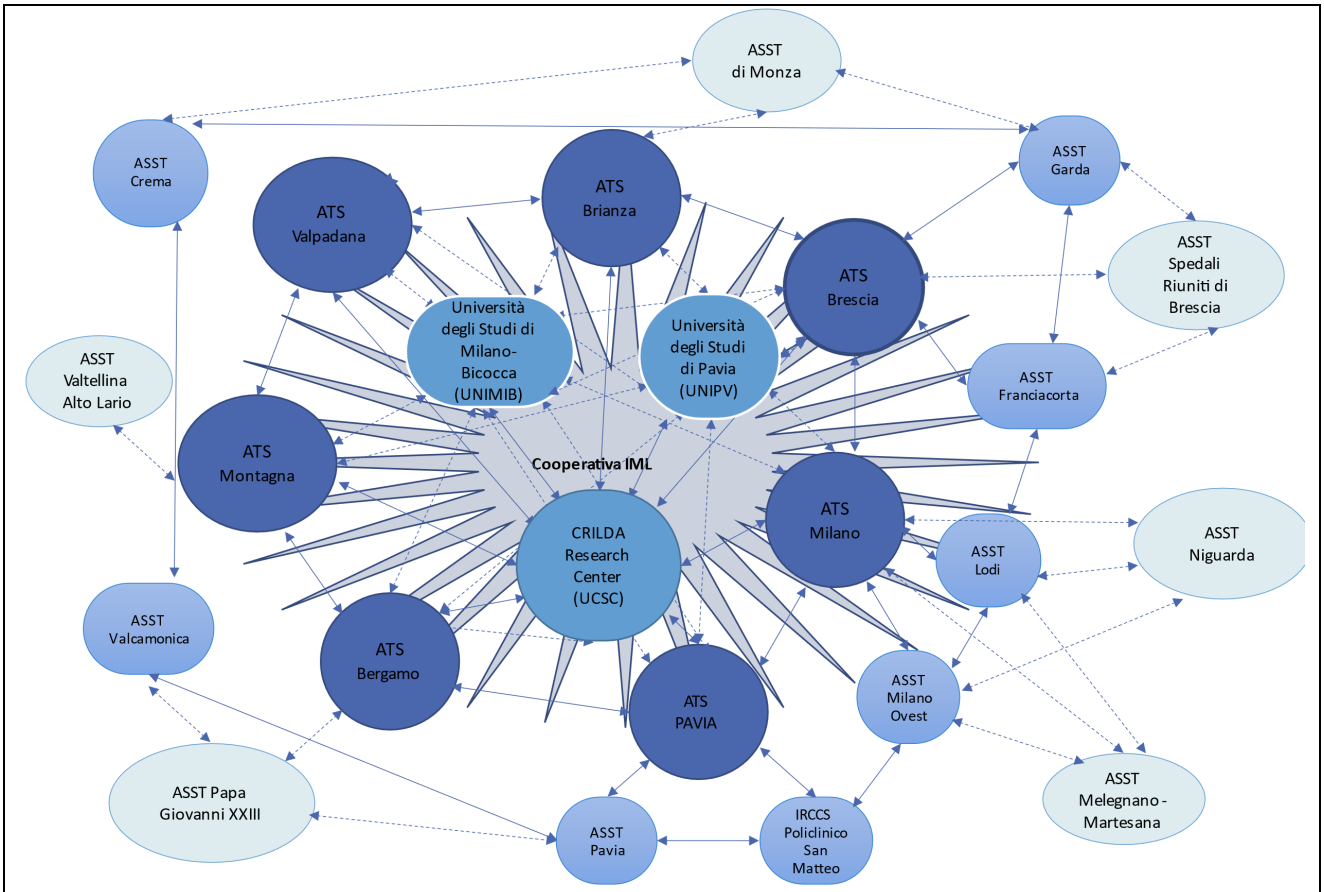
Describe all organizations involved in the project, their role, and the facilities provided. List partners, third parties and other organizations involved in the project. Describe the project's governance and how the scientific committee represent an add value for the project's management.

(maximum 15000 characters excluding figures, tables and pictures) - 12,945 *characters*

Partnership

The network of the project consists of 18 partners, 6 supporting institutions and an external service provider representing general practitioners as shown in Figure 1. A detailed description of all partners and institutions involved is provided below.

Figure 1 Composition of the Project Network



- ATS, ASST and IRCCS: ATS Milano – ASST Lodi, ASST Ovest; ATS Valpadana – ASST Crema; ATS Bergamo; ATS Brescia – ASST Garda, ASST Franciacorta; ATS Brianza; ATS della Montagna – ASST Valcamonica; ATS Pavia – ASST Pavia, IRCCS Policlinico San Matteo
- Universities: CRILDA Research Center at Università Cattolica del Sacro Cuore (UCSC), Department for Economic and Business Science of Università di Pavia (UNIPV), Centro Interdipartimentale Bioinformatics Biostatistics and Bioimaging Centre - B4 of Università Milano-Bicocca (UNIMIB)
- General Practitioners Cooperative – Iniziativa Medica Lombarda (IML)
- Supporting institutions: ASST Niguarda, ASST Melegnano Martesana, ASST Spedali Riuniti di Brescia, ASST Monza, ASST Papa Giovanni XXIII, ASST Valtellina e Alto Lario

The different partners will share data and competences to reach the objectives of the project, which will unfold in several directions. In particular, the ATSs will use their budget to provide the digital platform for data collection and merging of health administrative and clinical data, and to recruit a data manager for the duration of the project who will guarantee data quality and perform data extraction for the whole network. They will also perform the epidemiological studies and provide to ASSTs, IRCCS and GPs the list of patients to be included in the clinical follow-up. The partner ASSTs and IRCCS will perform the clinical follow-up of hospitalized patients, their budget to recruit temporary contract health professionals, while general practitioners will follow-up patients treated at home as an external contract service. The specialists from both partner ASSTs, ASSTs participating as supporting institutions, IRCCS and representatives from general practitioners' cooperatives will deal with the elaboration of protocols regarding the monitoring of PASC clinical manifestation, sharing it with other actors of the network.
The involved Universities will provide methodological support in the different phases of the project. UCSC, as leading partner, will coordinate the overall project, taking charge of several Project's tasks which are shared by all partners – such as the coordination of a Project manager, Audit services, as well as services that are provided by third parties to the Project (such as IML). These coordination tasks and additional services will be paid out from the Coordinator's budget. UCSC will also lead WP4 investigating the indirect effects of the epidemic on the provision of health care. In particular, using register data from partner ATSs,

the analysis will assess the reduction of outpatient services and screening tests due to the emergency phase, as well as the post-emergency congestion effects (supply side). Also, behavioral effects, such as the reluctance to visit hospitals during the pandemic, will be investigated (demand side) with the purpose of identifying and profile different categories of fragile patients in need of specific prevention, care, and rehabilitation pathways. To perform these tasks UCSC will use part of the budget to hire a contract-researcher for 12 months. UNIMIB will develop the integration of administrative and clinical data to perform a long-term evaluation on the resulting cohort, including the comparison between outcomes of patients enrolled or not in the PASC follow-up. UNIPV will identify the key management issues for the definition of a new organizational model for the management and monitoring of PASC patients, involving innovative patterns of collaboration among the different agents within the health-care system. Both UNIMIB and UNIPV will use their budget mainly to hire a contract-researcher for 12 months.
The project will file ethical approuval before one of the Partners' Ethical committee. Clearance by the Ethical committee will be the first action before the start of clinical activities. The studies conducted in the context of the present project will be performed according to EU regulation 2016/679 and EU directive 2016/680 (GDPR). Information about involved individuals will be stored and handled abiding to art. 13 EU regulation 2016/679 and to Italian privacy laws. Privacy of data will be guaranteed through the use of a GDPR-compliant digital infrastructure where the extracted variables from administrative data and the clinical data from the project will be stored. Specific subsets of data will be analyzed in the GDPR-compliant digital infrastructure of the Universities and the ATS. All data transfers between components of the network will be performed through high-security, GDPR-compliant systems. The Data Protection Officer of the ATS providing the digital infrastructure (Valpadana) will oversee the agreements for data sharing within the network.

PARTNERS

UNIVERSITA' CATTOLICA DI MILANO (UCSC) – Leading institution

The "Centro di Ricerca sul Lavoro Carlo Dell'Aringa" (CRILDA-UCSC) research center, directed by Claudio Lucifora (PI) is part of the Università Cattolica del Sacro Cuore which includes 14 faculties, 62 departments and 93 research centers. CRILDA gathers researchers in different fields, to design multi-disciplinary approaches in its research, evaluation and consultancy activities and offer all the facilities required for the development of high-quality research studies (e.g., rooms and furniture, high-speed internet access, and access to multiple resources). The ALTEMS School of Public health at Università Cattolica del Sacro Cuore will also cooperate, providing expertise in the analysis of Covid-19 data and management of public health system. The school during the pandemic has been leader in providing a weekly report on the diffusion of Covid-19 (see https://altems.unicatt.it/altems-covid-19) and a stress test on public health systems. Within this project, UCSC is the leading institution, responsible for WP4 as well as of the project design, its implementation and dissemination activities. It will coordinate other partners and will be responsible for the communication with Fondazione Cariplo.

UNIVERSITA' DEGLI STUDI DI MILANO-BICOCCA (UNIMIB)

Università degli Studi di Milano-Bicocca (UNIMIB) is a public University funded in 1998. It counts 14 departments and around 1000 researchers. The interdepartmental Bicocca Bioinformatics Biostatistics and Bioimaging Centre - B4 aims to bring together in a single University structure the methodologies and computational skills necessary to face the challenges of quantitative and personalized medicine, and to apply them for the enhancement and dissemination of multidisciplinary research in the area of life science. Within the present project, UNIMIB will provide support to the UCSC team in the development of the project and will be responsible for WP3.

UNIVERSITA' DEGLI STUDI DI PAVIA (UNIPV)

Università degli Studi di Pavia (UNIPV) is one of the world's oldest academic institutions, with its foundations existing as early as the 9th Century. It counts about 26,000 students, 1,800 researchers and administrative staff. The Department of Economics and Management and its 'Digita4good' Lab will support the research activities of the project. Digita4good promotes research on how digital data streams can support health-care management and emergency events, together with leading digital companies and international universities (https://www.digita4good.unipv.it/).

UNIPV will provide support to the UCSC team in the development of the project and will be responsible for WP5, while participating to the activities in WP2.

AGENZIE DI TUTELA DELLA SALUTE (ATS) – Agency for Health Protection
ATS Città Metropolitana di Milano (ATS-MI)
ATS Pavia (ATS-PV)
ATS Valpadana (ATS-VP)
ATS Bergamo (ATS-BG)
ATS Brescia (ATS-BS)
ATS Brianza (ATS-BR)
ATS Montagna (ATS-Montagna)

ATSs are public institutions of the Lombardy Region, which have the mission to put into practice the health plans devised by the Lombardy Region on their area of competence. They guarantee the provision of essential health services (*Livelli Essenziali di Assistenza - LEA*) through health-care facilities, both public and private. They also oversee the integration of health and social services provided by the public authorities.
Within the present project, ATSs will be responsible of and carry out WP1 and will be involved in WP2. ATSs also play a key role in providing access to health data registry (big data), as well as for the dissemination of results to stakeholders and general practitioners. ATS Milano will also participate in WP3. Moreover, ATS-MI, UCSC research team, UNIMIB and UNIPV already cooperated on a number of research projects, PhD programs and their research activities are regulated by different memorandum of agreement (MoA 2018-20 'UCSC & ATS-MI'; MoA 2017-20 'UCSC & FOND FERRERO'; Defap PhD program 'UCSC & UNIMIB', MoA 'UNIMIB & ATS-MI Scuola Specializzazione Statistica Sanitaria, MOA 2021-24 'UNIMIB & ATS-MI per tirocini curriculari').

AZIENDE SOCIO SANITARIE TERRITORIALI (ASST) – Local Health Care Public Body
ISTITUTO DI RICERCA E CURA A CARATTERE SCIENTIFICO (IRCCS) - Scientific Institute for Research, Hospitalization and Healthcare

ASST Crema (ASST-CR)
ASST Franciacorta (ASST-FRC)
ASST Garda (ASST-GRD)
ASST Lodi (ASST-LD)
ASST Milano Ovest (ASST-MIO)
ASST Pavia (ASST-PV)
ASST Valcamonica (ASST-VCM)
IRCCS Policlinico San Matteo (IRCCS-SM)

ASSTs are public institutions of the Lombardy Region, which provide inpatient and outpatient health services to the population of the territory they cover. They are articulated in hospital (Departments) and territorial (Districts) services, and they also coordinate the primary care and the pharmaceutical services part of the public National Health Care System. Within the project, ASSTs will be responsible of and carry out WP2 defining follow-up protocols, performing clinical follow-up, and being Involved in the interpretation of the results of the incidence analyses relating to the various syndromic manifestations. They will also implement the organizational models and digital health solutions developed for the follow-up of the PASC as part of the project. ASSTs will also participate in WP3 on a voluntary basis.

IRCCSs are biomedical institutions of relevant national interest, which drive clinical assistance in strong relation to research activities. Their mission is the continuous upgrade of healthcare. The IRCCS title is granted by Italian Department of Health to a very limited number of institutes throughout the nation. They are committed to be benchmark for the whole public health system for both the quality of patient care and the innovation skills in the field of organization. Within the project they will have the same role as ASSTs.

SUPPORTING INSTITUTIONS

Cooperativa IML

ASST Niguarda
ASST Melegnano Martesana

ASST Spedali Riuniti di Brescia
ASST Monza
ASST Papa Giovanni XXIII
ASST Valtellina e Alto Lario

SCIENTIFIC COMMITTEE

The scientific committee will include the lead researcher of each institution (Claudio Lucifora, Stefano Denicolai, Grazia Valsecchi, Anita Andreano, Pietro Perotti, Marco Villa, Alberto Zucchi, Luca Cavalieri d'Oro, Giovanni Maifredi, Anna Clara Fanetti, Vincenzo Belcastro, Stefano Rusconi, Giuseppe La Piana, Luigi Magnani, Anna Bussi, Gabriele Zanolini, Raffaele Bruno, Maurizio Morlotti) and Dr. Antonio Giampiero Russo as the coordinator of the activities of the ATSs. Moreover, clinicians representing the supporting ASSTs and members of the Cooperative of GPs IML, will be designated if the project will be funded. Among the supporting ASSTs there are some of the largest in Lombardy and most involved during COVID-19 epidemics (Niguarda, Monza, Bergamo Papa Giovanni XXIII, Brescia Spedali Riuniti) and their contribution will be valuable to the project, both in terms of practical experience and scientific knowledge. The scientific committee will meet at the beginning of the project, to determine its internal functioning, to validate the developed follow-up protocols, to examine the results of each work-package, and to approve dissemination initiatives.

Coordination and management

The scientific committee will coordinate all the activities and supervise the accomplishments of the project's tasks, through regular meetings, either in person or in web-conference, at least every month in the preliminary phase (months one to three), and every two months for the remainder of the project (months four to fifteen).

Steering committees with PIs and the representatives of ATSs and ASSTs will meet every 2-3 months to monitor the ongoing of the clinical follow-ups and the definition of the different protocols for PASC diagnostics, with the aim of sharing information, implementing awareness initiatives, and organizing participative discussions of the research results also at the local level.

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[maximum 50 publications]

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