REGISTRY PROTOCOL

Protocol Title:	International Registry of Healthcare Workers Exposed to COVID-19 Patients (UNITY Global)
Protocol Number:	CER-HCW-001
Protocol Version:	Version 1.1
Protocol Date:	11 June 2021
Sponsor:	Certara Inc.
Clinical Research Organization:	Parexel International

SPONSOR

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SIGNATURE PAGE

Declaration of Sponsor's Responsible Person

Title: International Registry of Healthcare Workers Exposed to COVID-19 Patients (UNITY Global)

This study protocol was subjected to critical review. The information it contains is consistent with the International Society for Pharmacoepidemiology Guidelines on Good Pharmacoepidemiology Practices.

_____ _____

Name: Roman Casciano Date
Title: Senior Vice President, Evidence and Access
Institution: Certara, Inc.

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Name: Craig Rayner Date
Title: President, Integrated Drug Development
Institution: Certara, Inc.

Declaration of the Study Co-leads

Title: International Registry of Healthcare Workers Exposed to COVID-19 Patients (UNITY Global)

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Study Co-lead

_____ _____

Name: Roman Casciano Date
Title: Senior Vice President, Evidence and Access
Organization: Certara, Inc.

Responsible Study Co-lead

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Name: Craig Rayner Date
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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin-converting Enzyme
AE	Adverse Event
ARB	Angiotensin II Receptor Blockers
BCG	Bacillus Calmette–Guérin
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
GPP	Good Pharmacoepidemiology Practices
HCW	Healthcare Worker
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
ICU	Intensive Care Unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRB	Institutional Review Board
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
SAC	Scientific Advisory Committee
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
WHO	World Health Organization

3 RESPONSIBLE PARTIES

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4 ABSTRACT

Protocol Title:	International Registry of Healthcare Workers Exposed to COVID-19 Patients (UNITY Global)
Protocol Number:	CER-HCW-001
Protocol Version:	Version 1.1.
Protocol Date:	11 June 2021
Author:	*To be confirmed*.
Sponsor:	Certara, Inc
Background:	Healthcare workers (HCWs) are integral in providing clinical care to COVID-19 patients. Due to the highly infectious nature of the SARS-CoV-2 virus known to cause COVID-19, rigorous infection prevention and control measures in healthcare facilities are needed to limit nosocomial (healthcare-associated) infections among HCWs, and preserve the ability of the healthcare system to handle the patient caseload. Several medicines (e.g., hydroxychloroquine, lopinavir) have been proposed as potentially valuable prophylaxis to help reduce the risk of infection among HCWs and others, however, limited evidence of their effectiveness exists in this setting.
Description:	The International Registry of Healthcare Workers Exposed to COVID-19 Patients (UNITY Global), is an international registry of approximately 10,000 healthcare workers in low- and middle-income countries experiencing increasing numbers of COVID-19 cases and commensurate increased exposure to the SARS-CoV-2 virus among their healthcare worker populations.
Aims and Objectives:	The aim of this registry is to generate real-world evidence in HCWs to potentially inform recommendations and policies on prevention measures, including prophylactic use of potential drug therapies in HCWs. **Primary Objective:** To assess the association of potential prophylactic treatments with reduced risk of COVID-19 (or SARS-CoV-2 infection) in HCWs caring for COVID-19 patients. **Secondary Objectives:** To characterize the type of potential prophylactic treatments, by dose and duration, overall, and by country/region/site and to explore the key factors (for example, use of personal protective equipment (PPE), HCW and healthcare facility characteristics, underlying co-morbidities, household history and COVID-19 exposure) modifying the risk of COVID-19 among HCWs.

Registry Enrolees:	The registry will enrol HCWs who are experiencing or are expected to experience ongoing and recurrent close contact with confirmed or clinically diagnosed COVID-19 patients. Recruitment for the registry will aim to enrol a representative distribution of HCWs on the front lines of diagnosing and caring for COVID-19 patients in both hospitals and community settings, as well as a balanced sample of HCWs receiving the most commonly administered putatively prophylactic drug regimens.
Data Collection:	The registry will collect information on a weekly basis from HCWs across a 12-week period following their first known exposure to confirmed or clinically diagnosed COVID-19 patients prior to or within 30 days after enrollment. Data collection will include the drug regimens being taken by the HCWs, information about their level of exposure to COVID-19 patients, their personal health status, and other factors such as the use of PPE which would likely impact their risk of developing a SARS-CoV-2 infection.
Analyses:	A standard pharmaco-epidemiological inferential analysis will be conducted treating the registry data as a cohort with dynamic exposure to both prophylactic treatment and to COVID-19 infected patients and adjusting for potential confounding. Crude and adjusted hazards ratios will be estimated for prophylactic regimens of interest and any observed impact on the risk of infection among HCWs based on all statistical inferential models will be reported.

5 AMENDMENTS AND UPDATES

DOCUMENT HISTORY		
Document	**Protocol Version**	**Date**
Amendment 1	1.1	11 June 2021
Original Protocol	1.0	08 June 2020

Amendment 1 (11 June 2021)

Overall rationale for the amendment: To adapt the protocol in accordance with the changing dynamics of the COVID-19 pandemic.

Specific changes to the protocol include:

LOCATION OF REVISION	DESCRIPTION OF REVISIONS	RATIONALE FOR REVISIONS
Background and Rationale: Section 6	**Previous text:** None **New text:** Several medicines (e.g., hydroxychloroquine, lopinavir) have been proposed as potentially valuable prophylaxis to help reduce the risk of infection among HCWs and others, however, limited evidence of their effectiveness exists in this setting.	In order to standardize the text throughout the document.
Research Methods: Sections 8.1, 8.2, 8.2.3, 8.3, 8.3.5, 8.5, 8.7.4, 8.9, and 8.10.1.	**8.1 Study Design** **Previous text:** However, serology testing for SARS-CoV-2 antibodies will be offered to the first 50% of participating HCWs per country, at enrollment and at the last follow-up (i.e. at Week 12). **New text:** However, serology testing for SARS-CoV-2 antibodies **may** be offered to **approximately** 50% of participating HCWs per country, at enrollment **(ranging from baseline up to Week 4 [African countries] and Week 8 [Pakistan])** and at the last follow-up (i.e. at Week 12).	As a result of the COVID-19 pandemic, the production of serology kits, and shipments to various countries were delayed. Additional COVID-19 delays were caused by regulations at customs, as well as availability of kit content at wholesalers. The optional serology sample collection does not form part of the endpoints and objectives of the study. Due to logistical constraints mentioned above, serology was not offered to the first 50% of healthcare workers per country, but rather a compliment of 50% of healthcare workers, upon kit availability. Within Pakistan, healthcare workers were offered serology, and were provided with testing kits, when the testing kits were available. It will therefore be allowed for the baseline sample to be collected from the following timepoints (ranging from baseline up to Week 8). Within the African continent, healthcare workers were offered

		serology, and were provided with testing kits when the testing kits were available. It will therefore be allowed for the baseline sample to be collected from the following timepoints (ranging from baseline up to Week 4).
	8.1 Study Design **Previous text:** Healthcare workers will be identified for participation via a central contact at participating healthcare facilities and directed to a website/mobile application allowing them to electronically consent and answer questions that would help assess their eligibility to participate. **New text:** Healthcare workers will be identified for participation via a central contact at participating healthcare facilities and directed to a website/mobile application allowing them to electronically consent **(in parallel, paper consents may be used, as per local requirements)** and answer questions that would help assess their eligibility to participate.	Updated section to incorporate local requirements of participating countries which was not known at the time of the initial protocol finalization.
	8.1 Table 1 Schedule of Assessments **Previous text:** None **New text:** COVID-19 vaccination **Footnote e:** From the time the questions on vaccination go live in the web application online survey, baseline vaccination information will only be collected for newly enrolled HCW and for HCWs who did not complete the survey prior to the addition of vaccination questions. **Footnote f:** As a result of the COVID-19 pandemic, the production of serology kits, and shipments to various countries were delayed. It will therefore be allowed for the	To collect up-to-date information on prophylactic treatments available at the time of study. **Footnote f:** As a result of the COVID-19 pandemic, the production of serology kits, and shipments to various countries were delayed. Additional COVID-19 related delays were caused by regulations at customs, as well as availability of kit content at wholesalers.

	baseline sample to be collected from the following timepoints (ranging from baseline up to Week 8).	
	8.1 Table 1 Schedule of Assessments **Previous text:** Electronic consent **New text:** Electronic/**paper (if applicable)** consent	Updated table to incorporate local requirements of participating countries which was not known at the time of the initial protocol finalization.
	8.2 Population and Setting **Previous text:** The study population comprises male and female HCWs, aged 18 years or older, working in healthcare facilities (e.g., acute care hospital) or in a community healthcare setting (e.g., clinic) in countries potentially to include Bangladesh, Ethiopia, Pakistan, Rwanda, South Africa, Zimbabwe and other countries depending on the status of the local COVID-19 epidemic, and the availability and usage patterns of potential prophylactic treatments. **New text:** The study population comprises male and female HCWs, aged 18 years or older, working in healthcare facilities (e.g., acute care hospital) or in a community healthcare setting (e.g., clinic) in **the following** countries**: Indonesia, Kenya, Nigeria,** Pakistan, **Senegal,** South Africa, **Uganda, Zambia, and** Zimbabwe**. The countries were selected based** on the status of the local COVID-19 epidemic, and the availability and usage patterns of potential prophylactic treatments.	List of countries updated as per study feasibility assessments.
	8.2.3 Healthcare Worker Enrollment **Previous text:** Healthcare workers who agree to participate will be directed to a website/mobile application allowing them to electronically consent and confidentially complete questionnaires (the details and frequency of these questions are provided in Section 8.1). **New text:** Healthcare workers who agree to participate will be directed to a website/mobile application allowing them to electronically consent **(in parallel, paper consents may be used, as per local requirements)** and confidentially complete questionnaires (the details and frequency of these questions are provided in Section 8.1).	Updated table to incorporate local requirements of participating countries which was not known at the time of the initial protocol finalization.

	8.2.3 Healthcare Worker Enrollment **Previous text:** For example, the registry will enroll approximately 75% of HCWs on a potential prophylactic therapy and approximately 3-4% will be community HCWs as they are not typically represented in other registries. **New text:** For example, the registry will enroll approximately 75% of HCWs on a potential prophylactic therapy.	To remove restrictions on the enrollment of community HCWs.
	8.3 Variables **Previous text:** The sections below include outcomes, treatment exposure and PPE use, COVID-19 exposure, and other variables to be measured and accounted for in the study analyses. **New text:** The sections below include outcomes, treatment exposure and PPE use, COVID-19 exposure, **COVID-19 vaccinations**, and other variables to be measured and accounted for in the study analyses.	To collect up-to-date information on prophylactic treatments available at the time of study.
	8.3.5 Other Covariates **Previous text:** None **New text:** COVID-19 Vaccinations – Convidicea (Ad5-nCoV) – CoronaVac (Sinovac) – Covaxin (BBV152) – EpiVacCorona (Vector Institute) – Janssen Pharmaceuticals (Johnson & Johnson) (Ad26.COV2.S) – Moderna COVID-19 Vaccine – Novavax (NVX-CoV2373) – Oxford-AstraZeneca COVID-19 Vaccine – Pfizer-BioNTech COVID-19 Vaccine – Sinopharm BBIBP-CorV – Sputnik V COVID-19 Vaccine – Other (to be specified)	To collect up-to-date information on prophylactic treatments available at the time of study.
	8.5 Study Size **Previous text:** At least 10,000 HCWs as determined by an expert panel, considering diversity of risk factors (e.g., healthcare system, geography,	In order to standardize the text throughout the document.

	interventions such as PPE and prophylactic therapies in use). **New text:** **Approximately** 10,000 HCWs as determined by an expert panel, considering diversity of risk factors (e.g., healthcare system, geography, interventions such as PPE and prophylactic therapies in use).	
	8.7.4 Primary Analysis **Previous text:** A standard pharmaco-epidemiological inferential analysis will be conducted treating the registry data as a cohort with dynamic exposure to both prophylactic treatment and to COVID-19 infected patients. Both crude and adjusted hazards ratios will be estimated. **New text:** A standard pharmaco-epidemiological inferential analysis will be conducted treating the registry data as a cohort with dynamic exposure to both prophylactic treatment and to COVID-19 infected patients **and adjusting for potential confounding.** Both crude and adjusted hazards ratios will be estimated **for prophylactic regimens of interest and any observed impact on the risk of infection among HCWs based on all statistical inferential models will be reported.**	In order to standardize the text throughout the document.
	8.9 Limitations of the Research Methods **Previous text:** None **New text:** Since the data for this study are self-reported by HCWs who may not complete all surveys, this could lead to incomplete/missing data. In addition, there are possibilities of errors in recording information or missing information due to technical errors in the website/mobile application. To mitigate this risk, weekly SMS reminders and emails will be sent to HCWs. There is also an option of follow ups via phone call with HCWs as and when required.	To account for incomplete dataset and technical issues.
	8.10.1 Scientific Advisory Committee **Previous text:** The Scientific Advisory Committee will meet regularly throughout the study, and will focus on evaluating emerging evidence,	Updated to clarify SAC requirements

	providing “report to stakeholders”, “public data lens” and making recommendations including: **New text:** The Scientific Advisory Committee will focus on evaluating emerging evidence, providing “report to stakeholders”, “public data lens” and making recommendations including:	
Protection of Human Subjects: **Section 9.2**	**9.2 Electronic Informed Consent** **Previous text:** Before each participant is admitted to the study, informed consent will be obtained electronically from the HCW according to the regulatory and legal requirements of the participating country. Record of this consent will be retained in the study database. **New text:** Before each participant is admitted to the study, informed consent will be obtained electronically from the HCW according to the regulatory and legal requirements of the participating country **(in parallel, paper consents may be required in certain countries, e.g.,: Uganda and Zimbabwe according to local regulations.).** Record of this consent will be retained in the study database **(or country specific binders which will be archived at site according to local regulations).**	Updated section to incorporate local requirements of participating countries which was not known at the time of the initial protocol finalization.
Appendix 2 **Detailed SOA**	**Previous text:** None **New text:** COVID-19 Vaccine, to be selected as applicable) Convidicea (Ad5-nCoV) CoronaVac (Sinovac) Covaxin (BBV152) EpiVacCorona (Vector Institute) Janssen Pharmaceuticals (Johnson & Johnson) (Ad26.COV2.S) Moderna COVID-19 Vaccine Novavax (NVX-CoV2373) Oxford-AstraZeneca COVID-19 Vaccine Pfizer-BioNTech COVID-19 Vaccine Sinopharm BBIBP-CorV Sputnik V COVID-19 Vaccine Other (to be specified)	To collect up-to-date information on prophylactic treatments available at the time of study.

	Previous text: Electronic consent **New text:** Electronic/**Paper (if applicable)** consent	Updated section to incorporate local requirements of participating countries which was not known at the time of the initial protocol finalization.
Throughout	Minor, therefore have not been summarized.	Minor updates for format and language as applicable were made throughout the protocol.

6 BACKGROUND AND RATIONALE

Healthcare workers (HCWs) are integral in providing clinical care to COVID-19 patients. Due to the highly infectious nature of the SARS-CoV-2 virus known to cause COVID-19, rigorous infection prevention and control measures in healthcare facilities are needed in order to limit nosocomial (healthcare-associated) infections.[1]

In the context of the COVID-19 pandemic, healthcare workers are increasingly exposed directly to SARS-CoV-2-infected patients, sometimes without the appropriate level of personal protective equipment (PPE) and are at a high risk of nosocomial infection. As of 08 April 2020, 22,073 HCWs from 52 countries were reported as severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 positive.[1] Several medicines (e.g., hydroxychloroquine, lopinavir) have been proposed as potentially valuable prophylaxis to help reduce the risk of infection among HCWs and others, however, limited evidence of their effectiveness exists in this setting.

The China Center for Disease Control and Prevention indicated that 1,688 (3.8%) cases of the 44,672 confirmed SARS-CoV-2 positive cases occurred among HCWs.[2] In Italy, 11% of 15,314 infections were reported in HCWs (as of 10 April 2020).[3] Considering the different reporting practices across countries and the lack of systematic reporting of COVID-19 in HCWs to the World Health Organization (WHO), the prevalence of SARS-CoV-2 infection is likely underestimated globally.[1] While the majority of COVID-19 cases in HCWs are reported as mild disease, severe outcomes, including deaths, have also been reported.[4,5,6,7,8]

Community-based approaches designed to minimize unnecessary contact between HCWs and febrile cases through home-based testing and follow-up can reduce the risk and burden on HCWs, especially in areas where viral febrile illnesses primarily circulate.[12] In the current COVID-19 pandemic, especially in lower- and middle-income countries, community-based HCWs may be at the forefront of diagnosing and caring for COVID-19 patients and experience substantial contact with potential SARS-CoV-2 infected people by the nature of their work. To our knowledge, these groups are likely to be underrepresented in the current ongoing research among HCWs, despite their importance to the public health infrastructure.[13]

In addition to the potential harm SARS-Cov-2 infection may cause to HCWs, it will reduce healthcare capacity at a time when it will be overstretched by severe COVID-19 cases. In the context of the paradigm of "flattening the curve" to reduce peak infections to below the ceiling capacity of the healthcare system, infection of HCWs will lower the ceiling capacity making it less likely that systemically meaningful reductions can be achieved.

Understanding infection in HCWs is fundamental to informing specific infection prevention and control measures needed to protect HCWs.[1] Relatedly, characterizing the risk and the related risk factors in HCWs exposed to SARS-CoV-2, and quantifying the association of potential prophylactic treatments (medications or treatments designed and used to prevent occurrence of SARS-CoV-2 infection) with reduced risk of COVID-19 is a high priority globally. Several registries have been developed in the US and Europe, but low- and middle-income countries are underrepresented at this time.[14]

An international registry of HCWs exposed to SARS-CoV-2 will provide fundamental information on the status and give an indication of the association of potential prophylactic and preventive measures. In addition, this registry could also be used to inform study rationales and designs for future research involving COVID-19 among HCWs. Furthermore, registry findings may also inform recommendations and policies on the prophylactic use of potential therapies in HCWs.

7 STUDY AIM AND OBJECTIVES

This is an international registry of HCWs exposed to SARS-CoV-2 while caring for confirmed or clinically diagnosed COVID-19 patients. The aim of this registry is to generate real-world evidence in HCWs to potentially inform recommendations and policies on prevention measures, including prophylactic use of potential drug therapies in HCWs.

7.1 Primary Objective

- To assess the association of potential prophylactic treatments with reduced risk of COVID-19 (or SARS-CoV-2 infection) in HCWs caring for COVID-19 patients.

7.2 Secondary Objectives

- To characterize the type of potential prophylactic treatments, by dose and duration, overall, and by country/region/site.
- To explore the key factors (for example, use of PPE, HCW and healthcare facility characteristics, underlying co-morbidities, household history and COVID-19 exposure) modifying the risk of COVID-19 among HCWs.

8 RESEARCH METHODS

8.1 Study Design

The UNITY Global Registry is designed as a comparative cohort study using longitudinal serial surveys implemented through a web/mobile application-based technology to encourage participation and facilitate rapid responses during this pandemic. The study population comprises adult male and female HCWs working in healthcare facilities (e.g., acute care hospital) or in a community healthcare setting (e.g., clinic) with ongoing and continuous exposure to confirmed or clinically diagnosed COVID-19 patients. Countries and healthcare facilities will be selected based on the availability of potential prophylactic treatments to prevent workplace infection from SARS-CoV-2. The association of potential prophylactic treatments will be measured using the WHO Ordinal Scale of Clinical Improvement.[9]

Individuals with workplace exposure to confirmed or clinically diagnosed COVID-19 patients prior to enrollment, or anticipated within 30 days after enrollment, will be eligible to participate. COVID-19 exposure is defined as per WHO classification.[9] The date of the HCW's first known exposure to a confirmed or clinically diagnosed case of COVID-19 is referred to as the "Index Date" (see Figure 2). Healthcare worker volunteers are ineligible if they had COVID-19 or symptoms highly suggestive of COVID-19 before the Index Date. However, at the time of enrollment, HCWs can be either SARS-CoV-2 positive (symptomatic or asymptomatic) or SARS-CoV-2 negative.

Healthcare workers will be identified for participation via a central contact at participating healthcare facilities and directed to a website/mobile application allowing them to electronically consent (in parallel, paper consents may be used, as per local requirements) and answer questions that would help assess their eligibility to participate. Information on potential prophylactic treatments used by HCWs will also be collected. The website/mobile application will prompt participants to provide entry-level information such as, demographics, underlying conditions, and exposure to COVID-19 patients.

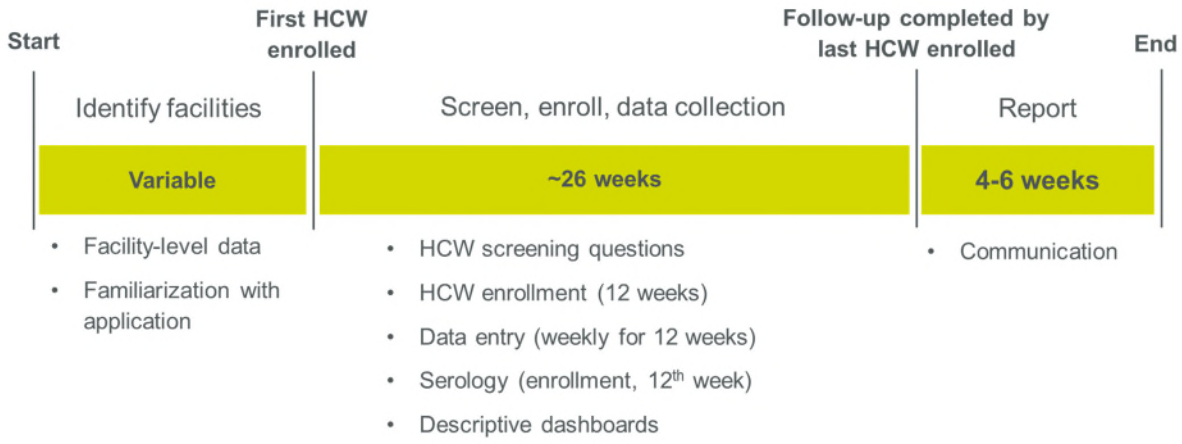
Healthcare workers will be expected to provide information on a weekly basis, for 12 weeks after enrollment. In case HCWs stop responding (after due diligence reminders), their secondary contacts (identified by the HCW, may be next of kin or other individuals informed of HCW's health status) will be approached. In case of conflicts, responses by HCWs will take precedence.

Enrollment will be monitored and potentially capped to ensure that the study enrolls an aggregate of at least 75% of HCWs who are taking a potential prophylactic therapy.

For details on the information collected and the overall study design, refer to Table 1, Table 2, Figure 1, and Figure 2, respectively.

This is a comparative observational cohort study; therefore, no preventive interventions, visits or laboratory tests are mandated. Dosing and duration of potential prophylactic treatment is at the discretion of the institution and/or healthcare provider, in accordance with regular local practice. However, serology testing for SARS-CoV-2 antibodies may be offered to approximately 50% of participating HCWs per country, at enrollment (ranging from baseline up to Week 4 [African countries] and Week 8 [Pakistan]) and at the last follow-up (i.e. at Week 12).

Figure 1 Study Schematic - High-level



HCW: Healthcare Worker

Figure 2 Study Schematic – Healthcare Worker Flow

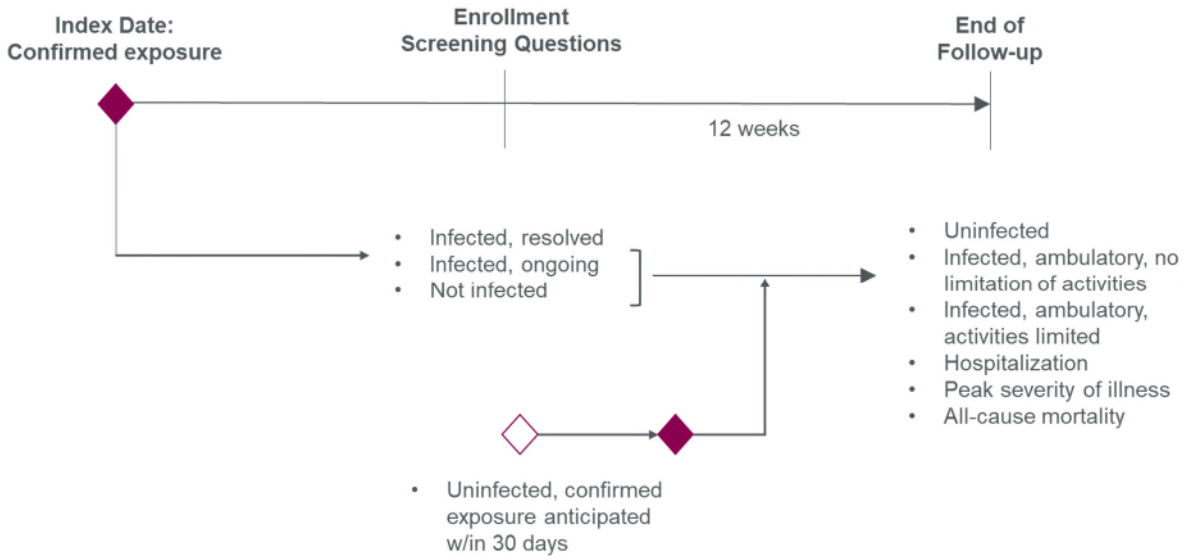


Table 1 Schedule of Assessments – Healthcare Worker Flow

Variable domain	At Enrollment	Weekly follow-up (until Week 12)[c]	
	HCW	HCW	Secondary Contact
Inclusion/eligibility criteria (screening questions/index date)	X	-	-
Electronic/paper (if applicable) consent	X	-	-
Demographics	X	-	-
Underlying conditions	X	-	-
Job characteristics	X	-	-
BCG vaccination history	X	-	-
Household history (COVID-19)	X	X	-
COVID-19 exposure	X	X	-
Prophylactic treatments	X	X	-
Concomitant medications	X	X	-
COVID-19 vaccination[e]	X	X	
PPE	X	X	-
COVID-19 symptoms	X	X	-
SARS-CoV-2 testing	X	X	-
Serology testing [f]	X	X[b]	
WHO Ordinal Scale for Clinical Improvement[d]	X	X	X[a]

BCG: Bacillus Calmette–Guérin; CoV: Coronavirus; HCW: Healthcare worker; PPE: Personal Protective Equipment; SARS: Severe acute respiratory syndrome; WHO: World Health Organization.

[a]: In case HCWs stop responding (after due diligence reminders), their secondary contacts will be approached. In case of conflicts, responses by HCWs will be considered.

[b]: Testing to be requested at last (Week 12) follow-up.

[c]: Or, time since last follow-up, whichever is greater.

[d]: Adapted, abbreviated version.

[e]: From the time the questions on vaccination go live in the web application online survey, baseline vaccination information will only be collected for newly enrolled HCW and for HCWs who did not complete the survey prior to the addition of vaccination questions.

[f]: As a result of the COVID-19 pandemic, the production of serology kits, and shipments to various countries were delayed. It will therefore be allowed for the baseline sample to be collected from the following timepoints (ranging from baseline up to Week 8).

Table 2 Schedule of Assessments – Facility-Level

Variable domain	Prior to study	End of study
Country, region	X	-
Urban or rural setting	X	-
Type of facility (public/private/community healthcare)	X	-
Teaching/university hospital or non-teaching	X	-
Capacity		
number of patients tested for COVID-19	X	X
number of COVID-19 patients treated	X	X
number of hospital beds (overall, ICU, emergency department)	X	X
number of exposed HCWs	X	X
number of HCWs tested for COVID-19	X	X
Number of HCWs who developed confirmed or clinically diagnosed COVID-19	X	X
Number of HCWs who died from COVID-19	X	X
Approved PPE use policy, and experience of PPE shortage	X	X
Approved prophylactic treatment policy	X	X
Shortage of COVID-19 related tests	X	X
BCG vaccination policy	X	X

HCW: Healthcare worker; PPE: Personal Protective Equipment; BCG: Bacillus Calmette–Guérin.

8.1.1 Primary Outcome

- Occurrence of SARS-CoV-2 infection among HCWs caring for COVID-19 patients, in terms of time, geography, healthcare setting, type of HCW.

8.1.2 Secondary Outcomes

- Occurrence of SARS-CoV-2 uninfected HCWs.
- Occurrence of SARS-CoV-2 infection with ambulatory status and no limitation of activities.
- Occurrence of SARS-CoV-2 infection with ambulatory status and limitation of activities.
- Occurrence of hospitalization due to COVID-19 illness with mild disease.
- Occurrence of hospitalization due to COVID-19 illness with severe disease.
- Occurrence of all-cause mortality.
- Type of prophylactic treatments by dose, frequency and duration, overall and by country/region/site.

8.1.3 Rationale for the Study Design

The disease landscape of COVID-19 is rapidly evolving. There is, however, a lack of data about the rate of infection in HCWs given the exposure to COVID-19 patients and the association of potential prophylactic treatments used by HCWs. A global registry comprising HCWs caring for COVID-19 patients will therefore be instrumental to generate real-world evidence to inform further studies involving characterization of PPE and potential prophylactic treatments and the risk of SARS-CoV-2 infection among HCWs.

The primary analyses in this registry are aimed at assessing the use and association of potential prophylactic treatments with COVID-19 in HCWs. The secondary analyses will explore potential risk factors for infection and other factors that may affect its association with potential prophylactic treatment therapies.

8.2 Population and Setting

The study population comprises male and female HCWs, aged 18 years or older, working in healthcare facilities (e.g., acute care hospital) or in a community healthcare setting (e.g., clinic) in the following countries: Indonesia, Kenya, Nigeria, Pakistan, Senegal, South Africa, Uganda, Zambia, and Zimbabwe. The countries were selected based on the status of the local COVID-19 epidemic, and the availability and usage patterns of potential prophylactic treatments.

Hospitals or healthcare facilities directly participating in the study in target countries of interest should have at least five COVID-19 cases at the time of establishing the registry. Institutions that participate in the study should be able to provide a list of HCWs exposed to COVID-19 patients.

As per the WHO definition[10], HCWs eligible for enrollment are limited, based on the high likelihood of being exposed to COVID-19 patients during patient care, to the following positions:

- Medical doctors*

- Clinical officers*
- Licensed physician assistant or nurse practitioner*
- Registered nurse (or equivalent)*
- Assistant nurse, nurse technician (or equivalent)*
- Phlebotomist
- Clinical pharmacist
- Clinical physical therapist
- Respiratory therapist
- Community healthcare worker

*These should include the following primary specialties:

- Surgery (all sub-specialties)
- Internal medicine (general)
- Pulmonology/critical care
- Emergency medicine
- Geriatrics
- Cardiology
- Infectious disease
- Anesthesiology
- Pediatrics
- Obstetrics/Midwifery
- Other

8.2.1 Inclusion Criteria

Healthcare workers will be entered into this study only if they meet ALL the following criteria:

- Healthcare workers aged ≥ 18 years.
- Healthcare workers must be exposed through ongoing and recurrent contact to a confirmed or clinically diagnosed COVID-19 patient prior to enrollment, or anticipated within 30 days after enrollment.
- Healthcare workers must consent to provide data for the registry and must be willing to be contacted/reminded about data entry at each follow-up time point.
- Healthcare workers must agree to provide a secondary contact for follow-up.

8.2.2 Exclusion Criteria

- A confirmed SARS-CoV-2 infection or clinically diagnosed COVID-19 prior to the first known exposure to confirmed or clinically diagnosed COVID-19 patient (Index Date).
- Participation in a 'blinded' clinical trial, i.e., unaware of exact treatment received as part of the clinical trial.

8.2.3 Healthcare Worker Enrollment

Healthcare workers from participating healthcare facilities and clinics will be recruited through a centralized effort within each facility/clinic. Healthcare workers who agree to participate will be directed to a website/mobile application allowing them to electronically consent (in parallel, paper consents may be used, as per local requirements) and confidentially complete questionnaires (the details and frequency of these questions are provided in Section 8.1).

Enrollment will be continuously monitored and potentially capped to ensure that the study proportionately enrolls HCWs according to country, type of HCW and status of prophylaxis. For example, the registry will enroll approximately 75% of HCWs on a potential prophylactic therapy.

This registry will remain open and will continue to enroll HCWs for as long as the pandemic continues regionally, or until otherwise determined by the Sponsor.

8.2.4 Healthcare Worker Withdrawal

HCWs may withdraw from the study (i.e., withdraw their consent) at any time.

HCWs may be required to withdraw at the discretion of the Sponsor in case of incorrect self-enrollment (failure to meet inclusion/exclusion criteria).

In the case of an HCW withdrawing consent through the study registry web form, the entry is recorded in the system. If the Sponsor and study team decide to withdraw the HCW, then they will track that decision in a study log that would be uploaded to the reporting database for analysis.

8.2.5 Healthcare Worker Identification Numbers

Participant identification numbers will be randomly generated 32-digit alphanumeric characters used to key code the patients into the Central Data Store for analysis.

8.3 Variables

The sections below include outcomes, treatment exposure and PPE use, COVID-19 exposure, COVID-19 vaccinations, and other variables to be measured and accounted for in the study analyses. Refer to Appendix 2 for further details.

8.3.1 Clinical Outcomes Variables

- WHO Ordinal Scale for Clinical Improvement of COVID-19 (adapted, abbreviated version)
    - SARS-CoV-2 (uninfected/infected)
    - Ambulatory status (limitation/no limitation of activities)
    - Hospitalized with no intensive care unit (ICU) or mechanical ventilation (mild)
    - Hospitalized with ICU and/or mechanical ventilation (severe)
    - Death

8.3.2 Prophylactic Treatment (Treatment Exposure)

- Types, intake frequency, and doses of prophylactic treatments
    - Treatment name
    - Date started
    - Date stopped
    - Dose (intake)
    - Duration of treatment
    - Dose frequency and dosing interval
    - Status (stopped/ongoing)
    - Reason for stopping (not available/side effects/expense/other)
    - Number of missed doses and reason (not available/side effects/expense/other)

8.3.3 History of Exposure to COVID-19 Patients

- At enrollment
    - Self-reported ongoing and recurrent exposure (yes/no)
    - WHO exposure definition (3 questions) (yes/no)
        - Direct patient care (yes/no)
        - Face-to-face contact (yes/no)
        - Present during aerosol-generating procedure (yes/no)
- Weekly follow-up
    - Self-reported ongoing and recurrent exposure (yes/no)
    - WHO exposure definition (3 questions) for past week

  - Days worked past week
  - Number of COVID-19 cases exposed to in the past week

8.3.4 Personal Protective Equipment Use

- At enrollment
  - Type and use of PPE prior to enrollment
- Weekly follow-up
  - Type and use of PPE at time of confirmed exposure(s) in the past week
  - Number of COVID-19 exposures in the absence of a mask
  - Longest COVID-19 exposure in the absence of a mask

8.3.5 Other Covariates

- COVID-19 symptoms (and date the symptoms begin)
  - Fever (temperature over 38°C)
  - Subjective fever (felt feverish)
  - Chills
  - Myalgia (muscles hurt or ache)
  - Rhinorrhea (runny or drippy nose)
  - Pharyngitis (sore throat)
  - Cough (new onset or worsening of chronic cough)
  - Dyspnea (hard to breathe or difficulty breathing)
  - Pneumonia
  - Nausea or vomiting
  - Headache or migraine
  - Abdominal pain (pain in tummy)
  - Asthenia (weakness or loss of strength)
  - Arthralgia (joint pain)
  - Anosmia (loss of smell)
  - Ageusia (loss of taste)
  - Blue coloring in toes
  - Diarrhea (two or more looser-than-normal stools in 24 hours)
- SARS-CoV-2 testing
  - Type of test, if known
    - PCR (positive/negative)
    - Antigen test (positive/negative)
    - Serology (immunoglobulin G [IgG] and/or immunoglobulin M [IgM], positive/negative or titer)
  - Date of test

- Household history (COVID-19)
    - Number of household contacts
    - Additional household member(s) exposed to COVID-19 (yes/no). If yes, how many?
    - Additional household member(s) with symptoms consistent with COVID-19 (yes/no). If yes, how many?
    - Additional household member(s) diagnosed with COVID-19 (yes/no). If yes, how many?
- Healthcare worker-level covariates
    - Demographics at entry
    - Underlying conditions and key co-morbidities
    - Job characteristics
    - Concomitant medications
    - Blood type
- Healthcare facility characteristics
    - Country, region
    - Urban or rural setting
    - Type of facility (public/private/community healthcare)
    - Teaching/university hospital or non-teaching
    - Capacity
        - number of patients tested for COVID-19
        - number of COVID-19 patients treated
        - number of hospitalized beds (overall, ICU, emergency department)
        - number of exposed HCWs
        - number of HCWs tested for COVID-19
    - Number of HCWs who developed confirmed or clinically diagnosed COVID-19
    - Number of HCWs who died from COVID-19
    - Approved PPE use policy, and experience of PPE shortage
    - Approved prophylactic treatment policy
    - Shortage of COVID-19 related tests
    - BCG vaccination policy
- Concomitant medications (other than for COVID-19)
    - Antibiotics (yes/no). If yes, please specify.
        - Azithromycin
        - Trimethoprim/sulphamethoxazole
        - Macrolide antibiotics (roxithromycin, clarithromycin, erythromycin)

    - Other antibiotics
  - Antimalarials (yes/no). If yes, please specify.
    - Hydroxychloroquine
    - Chloroquine
    - Sulfadoxine-pyrimethamine (SP)
    - Other antimalarials
  - Antiparasitics (yes/no). If yes, please specify.
    - Ivermectin (yes/no)
    - Other antiparasitics.
  - Antiretrovirals for Human Immunodeficiency Virus (HIV) (yes/no). If yes, please specify.
    - Lopinavir
    - Ritonavir
    - Tenofovir
    - Nelfinavir
    - Other antiretrovirals
  - Antivirals (yes/no). If yes, please specify.
    - Oseltamivir
    - Favipiravir
    - Arbidol
    - Anti-hepatitis C treatments
    - Remdesevir
    - Other antivirals
  - Medication for high blood pressure and cardiovascular disease (yes/no). If yes, please specify.
    - Angiotensin-converting enzyme (ACE) inhibitor (e.g., lisinopril, enalapril)
    - Angiotensin II receptor blockers (ARB) inhibitor (e.g., losartan, irbesarten)
    - Other anti-hypertensive for high blood pressure
    - Other medicine for high blood pressure and cardiovascular disease (e.g., antiarrhythmics, inotropes, chronotropes)
  - Nonsteroidal Anti-inflammatory Drugs (NSAIDs) e.g., Aspirin, Ibuprofen, Indomethacin, Celecoxib, Diclofenac (yes/no). If yes, please specify.
  - Botanicals (yes/no)
    - Artemisia teas (COVID Organics)
  - Immunocompromising drugs (yes/no). If yes, please specify.
    - Corticosteroids
    - Cancer chemotherapy

        - Cyclosporine
        - Drugs for autoimmune conditions such as lupus or rheumatoid arthritis, Crohn's disease
    - Changes in concomitant medications.
- COVID-19 vaccinations
    - Convidicea (Ad5-nCoV)
    - CoronaVac (Sinovac)
    - Covaxin (BBV152)
    - EpiVacCorona (Vector Institute)
    - Janssen Pharmaceuticals (Johnson & Johnson) (Ad26.COV2.S)
    - Moderna COVID-19 Vaccine
    - Novavax (NVX-CoV2373)
    - Oxford-AstraZeneca COVID-19 Vaccine
    - Pfizer-BioNTech COVID-19 Vaccine
    - Sinopharm BBIBP-CorV
    - Sputnik V COVID-19 Vaccine
    - Other (to be specified)

8.4 Data Sources

Primary data sources consist only of HCW-reported clinical information, obtained from HCWs completing an electronic data collection form. Secondary information from sites can be loaded to the Data Store for site time variable information, serology results, and HCW secondary point of contact feedback to the study team.

8.5 Study Size

Approximately 10,000 HCWs as determined by an expert panel, considering diversity of risk factors (e.g., healthcare system, geography, interventions such as PPE and prophylactic therapies in use).

8.6 Data Management

8.6.1 Data Collection

All eligible HCWs in the study facilities will be asked to enter the data in the registry via electronic data collection form.

Data will be collected at entry to the registry, and then weekly until 12 weeks after enrollment, death or lost to follow-up, whichever is earlier.

A secondary contact should be identified to be contacted to confirm status of HCWs in case of non-response/loss to follow-up.

Serology results from the laboratory will be loaded into the Local Data Store and merged with HCW contact information based on the participant identification numbers. Notification of results may be sent to the HCWs over secure link.

Data security and privacy is a key part of the application design:

- The Application has received a full penetration test from an accredited third party to cover cyber security threats.
- Data is segregated between the collection nodes and analysis nodes. Only information technology support staff have access to the data in the nodes for the express purposes of server support.
- All data on the analysis platform is tokenized with a unique patient token generated on the node. This tokenization uses a powerful salted hash algorithm (a document explaining this process may be reviewed if necessary but cannot be released for security reasons).
- Access to the data platform is controlled by Azure Active Directory accounts managed by the Parexel Support team.
- Access to the Application can only be achieved by end user registration using a set of industry leading authentication providers.
- The application has a unidirectional data flow from the node to the analysis platform so there is no risk of horizontal escalation issues.

A logical model of the data from the Central Data Store will be created in Microsoft Power BI to allow the study team to create dashboards and run global analysis on the de-personalized data. Additional tables can be added for Site data, Site timestamped variable records, secondary point of contact feedback to the Data Store to enable longitudinal analysis of co-variants

8.6.2 Archiving Study Records

According to International Society for Pharmacoepidemiology Guidelines on Good Pharmacoepidemiology Practices (GPP), the study archive will be maintained for at least 5 years after final report or first publication of study results, whichever comes later.

8.7 Data Analysis

A separate statistical analysis plan (SAP) will be produced, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final study report.

8.7.1 General Considerations

A number of key variables will be defined within the SAP, based on the data depth actually collected and on inputs from the Scientific Advisory Committee (SAC) members and from the local clinical experts. Those variables include e.g.,:

- Outcomes variables (confirmed versus clinically diagnosed).
- Variables defining intensity of exposure to COVID-19 infected patients over time.
- Variables defining exposure to potential prophylactic treatments imputable to a given outcome (e.g., cumulative or not, AUCs or dose over time, lagged effect).
- Switching or treatment interruption events.

Subpopulations to consider will also be discussed and detailed in the SAP.

Most analyses will be conducted using SAS or R software packages.

8.7.2 Analysis Population

The total pooled study population from all facilities will form the primary population for analysis.

Subgroup, stratified, and sensitivity analyses will also be defined in the SAP.

8.7.3 Descriptive Analyses

Prior to implementing the analysis to address the primary objectives of the study, descriptive analyses will be carried out to understand the main features and patterns in the population and in the data collected.

Crude numbers for each outcome will be displayed over time and as cumulative risks.

Study population characteristics will first be tabulated at index date and over time. Likewise, variables measuring exposure to potential prophylactic treatment and to COVID-19 patients over time.

Continuous variables over time will be described using summary statistics including mean, median, minimum and maximum, as well as box plots. Scores distribution over time will be displayed and Kaplan-Meier estimates will be calculated, and curves be plotted for each time-to-event outcome.

The observed incidence weekly rates of PCR-confirmed symptomatic COVID-19 and of COVID-19-related hospitalizations and deaths will be tabulated over weeks by facilities and compared according to prophylactic exposure in the study or against comparative controls.

Applications of estimated propensity scores will be employed to explore differences between HCWs' profiles exposed versus non-exposed to potential prophylactic treatments. Estimated propensity score distributions will be displayed over weeks and a concordance analysis performed to detect any trend over time.

Stratified pooled analyses at country level will also be displayed.

8.7.4 Primary Analysis

A standard pharmaco-epidemiological inferential analysis will be conducted treating the registry data as a cohort with dynamic exposure to both prophylactic treatment and to COVID-19 infected patients and adjusting for potential confounding.

Both crude and adjusted hazards ratios will be estimated for prophylactic regimens of interest and any observed impact on the risk of infection among HCWs based on all statistical inferential models will be reported.

Outcomes will be adjudicated to exposure time based on prior decision rules agreed with the SAC. Hazards for each subject-week will be compared and adjusted for exposure to prophylaxis over time, exposure to COVID-19 positive patients over time and to other covariates, accounting for subject-level clusters. Repeated time-to-event analyses with competing risk will be carried out.

Handling of missing data and unexplained drop-outs will be discussed with the SAC. Interaction terms to be considered will also be discussed with the SAC and clinicians.

Matching or other balancing methods such as estimated propensity score matching, inverse probability weighting or marginal structural methods, or alternative methods, will be considered to potentially address the identified biases and allow for evaluation of association.

In case the number of infection cases is lower than anticipated to allow for such analyses, matched case-control analyses will also be considered.

8.7.5 Secondary Analyses

All time-to-event secondary analyses will be conducted similar to the primary analysis.

They include:

- Time to clinical events (each defined by the WHO severity score or proxies to be defined).
- Time to switch or prophylaxis interruption.

Other derived variables such as time in hospitalization will be analyzed via generalized mixed effect models.

8.7.6 Sensitivity Analyses

Among the sensitivity analyses, the adjusted analyses of the primary outcome will be replicated:

- According to the subgroup of HCWs for which PCR-confirmed absence of infection at index date is demonstrated.
- According to the subgroup of HCWs for which serology results are available at entry and follow-up.
- Using the infection status and timing as self-reported only.
- Imputing unexplained drop-outs as events.
- According to the time from index date to entry in the registry date.

As part of a risk mitigation plan and for further insights generation, e.g., in the case of low number of events or unexpectedly low exposure to potential prophylactic treatments, alternative approaches will be considered to maximize the power and enhance the robustness of the proposed study. In this case, additional information e.g., from published local data could be leveraged using Bayesian modelling approach on the incidence dynamics modelling and association analyses, together with impact assessments.

8.7.7 Determination of Sample Size

The targeted sample size of approximately 10,000 HCWs assumes that 20% of the study population are non-exposed to potential prophylactic treatments, with a baseline risk of SARS-CoV-2 infection in the study period of 10% (for unexposed: not treated with potential prophylactic treatment). A total of N=10,000 allows for 80% power to identify an effect size of Relative Risk = 0.78.

8.8 Quality Control

8.8.1 Data Quality Assurance

The participants themselves will directly enter all study data on electronic web data entry form in a secure registry system. To the best of the Sponsor's ability, data logic and validation checks will be configured in the platform so that participants will receive warning messages at time of entry of inconsistent or invalid entries, in order to ensure quality and completeness of data.

After verification of eligibility and study enrollment, the self-reported data will not be queried for clarification or correction by the Sponsor after a participant's submission of the electronic web data form into the registry.

8.8.2 Access to Source Data

All data for this study are self-reported by the HCW and collected via the website/mobile application, and therefore there will be no source documents for monitoring.

8.9 Limitations of the Research Methods

As this is an observational study based on self-reported information from HCWs, there are several potential limitations and biases, as follows:

- Selection bias, either in the selection of sites/participants for the study (primarily affecting the external validity of the study) or treatment selection (i.e., non-randomized treatment selection affecting primarily internal validity). To minimize the impact of selection bias in the selection of participants, in each healthcare facility, the list of exposed HCWs will be obtained and all eligible HCWs will be offered enrollment.
- The inability to conduct probability sampling of sites/participants within sites will diminish the ability to generalize the findings from the study sample to the HCW population of inference.
- Survival bias may occur if eligible HCWs who developed COVID-19 were less or more likely to participate in the registry, or with inability of the registry to capture HCWs who died from COVID-19. This may lead to under- or over-estimation of the risk of COVID-19 based on the use of prophylactic treatment. To assess the impact of this bias, a metadata of healthcare facility-level variables will be collected at time of the registry establishment and at the end of the study, including number of exposed to COVID-19 HCWs, number of HCWs who developed COVID-19 and who died from COVID-19 at each participating healthcare facility.
- Similar bias may occur in case of differential lost to follow-up of HCWs based on COVID-19 status during follow-up. The inclusion of secondary contacts will allow to at least partially address the impact of this bias. Also, the proportion of HCWs lost to follow-up, including based on their risk profile and the use of prophylactic treatment, will be described.
- This study also allows for the enrollment of HCWs who have had a recent infection with recovery or ongoing symptoms at the time of enrollment, and HCWs without such a history and who are asymptomatic at the time of enrollment. While this approach facilitates faster enrollment and/or a greater number of HCWs to be

enrolled, a form of systematic measurement error called recall bias may result from an attempt to collect data retrospectively from those with a recent history of COVID-19. However, this potential source of bias will be assessed based on evaluations of facility-level data and stratified assessments of HCWs according to their index date (i.e., duration from the first known exposure to COVID-19 patients to the date of enrollment).

- All information is self-reported, and there is no mechanism to verify the accuracy of information entered into the web-application. Relatedly, the reporting of outcomes of hospitalization and death are dependent on the reliable participation of a secondary contact, who may be difficult to contact in the case of an HCW's death.
- Association of compared therapies may be confounded by non-random treatment selection/allocation that may have its provenance in unknown mechanisms associated with confounding by indication and channeling bias, among others. These may at least, in part, be addressed through the use of causal graphical models in association with appropriate statistical cohort balancing techniques, such as propensity score analysis and matching, and inverse probability weighted estimators, to be detailed in the SAP.
- The study may also be affected by protopathic bias in which the timing of, for example, formal diagnosis with regard to when symptoms and treatment occurs can result in incorrect causal inference regarding the effect of the treatment exposure on the risk of the outcome. A common general example is when patients are prescribed a drug to address disease symptoms ahead of the formal diagnosis of the disease which can lead one to incorrect inference regarding the effect of the treatment. Sensitivity analyses will be conducted among the subgroup of HCWs for which PCR-confirmed absence of infection at index date is demonstrated, and according to the subgroup of HCWs for which serology results are available.
- Since the data for this study are self-reported by HCWs who may not complete all surveys, this could lead to incomplete/missing data. In addition, there are possibilities of errors in recording information or missing information due to technical errors in the website/mobile application. To mitigate this risk, weekly SMS reminders and emails will be sent to HCWs. There is also an option of follow-ups via phone call with HCWs as and when required.

8.10 Other Aspects

8.10.1 Scientific Advisory Committee

A SAC will act in an advisory capacity to the Sponsor to provide guidance to the study design, conduct, analysis methodology and to support its successful completion. The Scientific Advisory Committee will focus on evaluating emerging evidence, providing "report to stakeholders", "public data lens" and making recommendations including:

- Strategies to optimize data collection, recruitment of HCW populations and potential real-world prophylactic therapies.
- Signals to escalate (association, safety, sub-population issues).

8.10.2 Transparency

To facilitate updates on study progress, SAC endorsed summary level and de-identified data evolving from the progress of the UNITY Global Registry will be communicated intermittenly on COVIDpharmacology.com.

9 PROTECTION OF HUMAN SUBJECTS

9.1 Good Pharmacoepidemiology Practices

The procedures set out in this study protocol are designed to ensure that the Sponsor and Study Lead abide by the principles of the International Society for Pharmacoepidemiology GPP guidelines.[11] The study also will be carried out in keeping with local legal requirements.

9.2 Electronic Informed Consent

Before each participant is admitted to the study, informed consent will be obtained electronically from the HCW according to the regulatory and legal requirements of the participating country (in parallel, paper consents may be required in certain countries, e.g.,: Uganda and Zimbabwe according to local regulations.). Record of this consent will be retained in the study database (or country specific binders which will be archived at site according to local regulations).

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), and signed by all participants subsequently enrolled in the study as well as those currently enrolled in the study.

9.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/IEC/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting participant risk) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.4 Confidentiality

All study findings and documents will be regarded as confidential. The Study Lead and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participants must be maintained. Study Leads shall ensure that personal identifiers will be removed from any study files that are accessible to non-study personnel in accordance with applicable laws and regulations. Participants will be identified in documents submitted to Parexel by their identification number, initials and/or birth date,

not by name. Documents not to be submitted to Parexel that identify the participant (e.g., the signed informed consent) must be maintained in confidence by the Study Lead.

9.5 Duration of the Study

The registry will remain open in different regions of the world for as long as the pandemic continues regionally.

For an individual participant, the maximum duration of participation in the study will be up to 12 weeks.

The entire study will end 12 weeks after the last-participant-in date.

9.6 Premature Termination of the Study

The study may be terminated early at the Sponsor's discretion. Conditions that may warrant termination include:

- Failure to enroll participants at an acceptable rate.
- A decision on the part of the Sponsor to suspend the study for administrative reasons.
- Ethical reasons.

10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

No AEs/adverse reactions will be collected during this study.

There are no physical risks to the participants in the study given the observational nature of the study design, apart from the minimal risk for obtaining blood/serology for SARS-COV-2 testing. A key risk to participants is a potential breach of confidentiality of the medical record information and the associated privacy. However, this risk is mitigated due to the data privacy measures incorporated in the web application system to key code participant data on the central reporting database accessible by the study team for data analysis.

If any unanticipated problems related to the study involving risks to participants or others happen during the course of this study, these will be reported to the IRB/IEC in accordance with all applicable IRB/IEC, local, and regulatory requirements. Any participant who believes that a serious risk may be associated with exposure to any prophylactic/concomitant treatment during the course of this study must report the AE to the manufacturer of the treatment, in accordance with applicable regulatory requirements.

Unanticipated problems that do not involve risks to participants or others will be summarized in narrative or other format and submitted to the IRB/IEC at the time of continuing review, if required.

11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Near real-time descriptive analytics dashboard will be made available in a continuous manner to provide a high-level view of pre-defined study variables/data. Additionally, emerging data on COVID-19 will be publicly shared, as appropriate.

The study findings may be disseminated if they are found to be of scientific or public health importance. Study results may be included in abstracts sent to scientific congresses. Specific plans for disseminating and communicating the study results will be produced when the results are available.

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Appendix 1: WHO Ordinal Scale for Clinical Improvement [9]

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Note: This scale has been used as a basis and adapted for the abbreviated version being employed in this study.

Appendix 2: Detailed SoA

Variable domain	At Enrollment	Weekly follow-up (until Week 12)	
	HCW	HCW	Contact
Inclusion/eligibility criteria			
Screening questions	X	-	-
Index date (date of first COVID-19 exposure)	X	X	-
Electronic/Paper (if applicable) consent	X	-	-
Demographics			
Contact information	X	-	-
Secondary contact	X	-	-
Facility	X	-	-
Date of birth (Age)	X	-	-
Gender	X	-	-
Weight	X	-	-
Height	X	-	-
Race	X	-	-
Blood type	X	-	-
Smoking status (current/past/never smoked)	X	-	-
BCG vaccination history (date, time period)	X	-	-
WHO Ordinal Scale for Clinical Improvement of COVID-19 (adapted, abbreviated version)			
SARS-CoV-2 (uninfected/ infected)	X	X	X
Ambulatory status (limitation/no limitation of activities)	X	X	X
Hospitalized with no ICU or mechanical ventilation (mild)	X	X	X
Hospitalized with ICU or mechanical ventilation (severe)	X	X	X
Death	-	-	X
Prophylactic treatments (treatment exposure)			
Treatment name	X	X	-
Date started	X	X	-
Date stopped	X	X	-
Dose (intake)	X	X	-
Duration of treatment	X	X	-
Dose frequency and dosing interval	X	X	-
Status (stopped/ongoing)	X	X	-
Reason for stopping (not available/side effects/ expense/other)	X	X	-
Number of missed doses (yes/no)	X	X	-
If yes, reason? (not available/side effects/expense/other)	X	X	-
History of exposure to COVID-19 patients			
Self-reported ongoing and recurrent exposure (yes/no)	X	X	-
WHO exposure definition (3 questions) (yes/no)	X	X	-
Direct care to COVID-19 patient (yes/no)	X	X	-
Face-to-fact contact (yes/no)	X	X	-
Present during aerosol-generating procedures (yes/no)	X	X	-
Days worked past week	-	X	-
Number of COVID-19 cases exposed to in the past week	-	X	-
Personal Protective Equipment			
Mask (N95 respirator mask or other) (if yes, always/not always)	X	X	-
Eye protection/goggles/face shield (if yes, always/not always)	X	X	-
Gown (if yes, always/not always)	X	X	-
Gloves (if yes, always/not always)	X	X	-
If "not always" or "no" for mask:			

Number of COVID-19 cases exposed to in the absence of a mask in the prior week	-	X	-
Longest COVID-19 exposure in the absence of a mask	-	X	-
COVID-19 symptoms			
Develop symptoms (yes/no), if yes – date the symptoms begin:	X	X	-
Fever (temperature over 38°C)	X	X	-
Subjective fever (felt feverish)	X	X	-
Chills	X	X	-
Myalgia (muscles hurt or ache)	X	X	-
Rhinorrhea (runny or drippy nose)	X	X	-
Pharyngitis (sore throat)	X	X	-
Cough (new onset or worsening of chronic cough)	X	X	-
Dyspnea (hard to breathe or difficulty breathing)	X	X	-
Pneumonia	X	X	-
Nausea or vomiting	X	X	-
Headache or migraine	X	X	-
Abdominal pain (pain in tummy)	X	X	-
Asthenia (weakness or loss of strength)	X	X	-
Arthralgia (joint pain)	X	X	-
Anosmia (loss of smell)	X	X	-
Ageusia (loss of taste)	X	X	-
Blue coloring in toes	X	X	-
Diarrhea (two or more looser-than-normal stools in 24 hours)	X	X	-
SARS-CoV-2 testing			
Tested? (yes/no)	X	X	-
Type of test	X	X	-
PCR (positive/negative)	X	X	-
Antigen test (positive/negative)	X	X	-
Serology (IgG and/ or IgM, positive/negative or titer)	X	X	-
Date of test	X	X	-
Serology testing	X	X	-
Household history (COVID-19)			
Number of household contacts	X	X	-
Additional household member(s) exposed to COVID-19 (yes/no) If yes, how many?	X	X	-
Additional household member(s) with symptoms consistent with COVID-19 (yes/no) If yes, how many?	X	X	-
Additional household member(s) diagnosed with COVID-19 (yes/no) If yes, how many?	X	X	-
Underlying conditions and key morbidities			
Chronic lung disease	X	-	-
Diabetes mellitus	X	-	-
Cardiovascular (heart) disease	X	-	-
Chronic renal (kidney) disease	X	-	-
Chronic liver disease	X	-	-
Immunocompromised condition (HIV/AIDS, organ transplant, other)	X	-	-
Tuberculosis	X	-	-
Neurologic/neurodevelopmental	X	-	-
Hypertension (high blood pressure)	X	-	-
History of stroke	X	-	-
Other chronic diseases	X	-	-
If female, currently pregnant	X	-	-
If female, currently breastfeeding/lactating	X	-	-
Job characteristics			
Type of healthcare work	X	-	-

Primary work location (ED, ICU, Medical floor)	X	X	-
Number of hours with patients	X	X	-
Concomitant medications (other than for COVID-19)			
Antibiotics (yes/no)	X	X	-
Antimalarials (yes/no)	X	X	-
Antiparasitics (yes/no)	X	X	-
Antiretrovirals for HIV (yes/no)	X	X	-
Antivirals (yes/no)	X	X	-
Medication for high blood pressure and cardiovascular disease (yes/no)	X	X	-
Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (yes/no)	X	X	-
Botanicals (yes/no)	X	X	-
Immunocompromising drugs (yes/no)	X	X	-
COVID-19 vaccine (to be selected as applicable)			
Convidicea (Ad5-nCoV)	X	X	
CoronaVac (Sinovac)	X	X	
Covaxin (BBV152)	X	X	
EpiVacCorona (Vector Institute)	X	X	
Janssen Pharmaceuticals (Johnson & Johnson) (Ad26.COV2.S)	X	X	
Moderna COVID-19 Vaccine	X	X	
Novavax (NVX-CoV2373)	X	X	
Oxford-AstraZeneca COVID-19 Vaccine	X	X	
Pfizer-BioNTech COVID-19 Vaccine	X	X	
Sinopharm BBIBP-CorV	X	X	
Sputnik V COVID-19 Vaccine	X	X	
Other (please specify)	X	X	

Appendix 3: List of Prophylactic Treatments

Select ALL that apply

1. Chloroquine - specify dose and interval
2. Hydroxychloroquine - specify dose and interval
3. Azithromycin - specify dose and interval
4. Lopinavir/ritonavir - specify dose and interval
5. Ivermectin - specify dose and interval
6. Other 1 – specify therapeutic, dose and interval
7. Other 2 – specify therapeutic, dose and interval
8. Other 3 – specify therapeutic, dose and interval

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Reason for signing: Approved	Name: Roman Casciano Role: Sponsor Date of signature: 17-Jun-2021 16:41:02 GMT+0000

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