



**What is the recovery rate and risk of long-term consequences following a diagnosis of COVID-19? – a harmonised, global longitudinal observational study protocol**

**ISARIC\* COVID-19 Global follow up working group**

Louise Sigfrid, T. Drake, D. Munblit, J.C.Holter, A.B. Kildal, E. Jesudason, W.S Lim, J. Rello, M. Dryden, W. Jassat, J. H. Amuasi, F. Bozza, C.Palmieri, L.F. Reyes, M. Cevik, C.D. Russell, A.Ho, L.Turtle, Beltrame, K. Hann, I.R. Bangura, R. Fowler, S. Lakoh, C. Berry, D.J. Lowe, J. McPeake, M. Hashmi, A.M. Dyrhol-Riise, C.Donohue, D.R. Plotkin, H. Hardwick, N. Elkheir, N. Lone, L. Blumberg, A.B. Docherty, E.M. Harrison, J.K. Baille, G. Carson, M.G. Semple, J.T. Scott

Study co-leads: Dr. Janet Scott and Dr. Louise Sigfrid, ISARIC Global support centre, Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK Contact e-mail: [louise.sigfrid@ndm.ox.ac.uk](mailto:louise.sigfrid@ndm.ox.ac.uk)

**Healthcare sites globally are invited to join this open access global collaboration to forward knowledge into Covid-19. For an interest in joining, to access the electronic database or for further information, please contact us at: [ncov@isaric.org](mailto:ncov@isaric.org)**

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**Summary**

Very little is known about possible clinical sequelae that may persist after resolution of the acute Coronavirus Disease 2019 (COVID-19). A recent longitudinal cohort from Italy including 143 patients recovered after hospitalisation with COVID-19 reported that 87% had at least one ongoing symptom at 60-day follow-up. Early indications suggest that patients with COVID-19 may need even more psychological support than typical ICU patients. The assessment of risk factors for longer term consequences requires a longitudinal study linked to data on pre-existing conditions and care received during the acute phase of illness. The primary aim of this study is to characterise physical and psychosocial sequelae in patients post-COVID-19 hospital discharge. Secondary aims include estimating risk factors for longer term sequelae and long-term patient outcomes. We invite hospitals and healthcare centres globally to join this open-access, collaborative study.

*Methods and analysis*

This is an international open-access prospective, observational multi-site study. This protocol is linked with the International severe acute respiratory and emerging infection consortium (ISARIC) and the World Health Organisation's (WHO) clinical characterisation protocol, which includes patients with suspected or confirmed COVID-19 during hospitalisation. This protocol will follow up a subset of patients with confirmed COVID-19 using standardised surveys to measure longer term physical and psychosocial sequelae. The data will be linked with the acute phase data. Statistical analyses will be undertaken to characterise groups most likely to be affected by sequelae of COVID-19. The open access follow up survey can be used as a data collection tool by other follow up studies, to facilitate data harmonisation, and to identify sub-sets of patients for further in-depth follow up .

*Ethics and dissemination*

This collaborative, open-access study aims to characterise the frequency of and risk factors for long-term sequelae in different populations worldwide. The protocol and survey are open access to enable low resourced sites to join the study, to facilitate global standardized, longitudinal data collection. The outcomes of this study will inform strategies to prevent long term consequences; inform clinical management, interventional studies, rehabilitation, and public health management to reduce overall morbidity and improve long term outcomes of COVID-19.

### **Strengths and limitations of this study**

- This is an open-access protocol and data collection forms to facilitate standardised, multisite data collection to forward knowledge into long term consequences of COVID-19.
- This study aims to inform strategies to prevent longer term sequelae; inform clinical management, rehabilitation, and public health management strategies to reduce morbidity and improve outcomes.
- The protocol will be used to follow up a sub-set of patients, already included in the existing ISARIC cohort of more than 88, 463 individuals hospitalized with COVID-19 across 42 countries (as of 4 October 2020).
- The follow up data will be linked with acute-phase data already documented using the ISARIC/WHO standardized Core- or RAPID case report forms (CRFs).
- The data collection tool is developed to facilitate wide dissemination and uptake with limited resources, to mitigate resources limitations during the pandemic.

### **Introduction**

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, can lead to a diverse range of clinical manifestations, ranging from an asymptomatic infection to an acute respiratory distress syndrome, and multiorgan failure with high risk of mortality (1). It is established that SARS-CoV-2 not only infects the respiratory tract but that ensuing viral replication and immune response may also affect other organs, which can lead to a risk of heart, renal and liver injury, in addition to an acute systemic inflammatory response and accompanying circulatory shock (2-4). While most people have uncomplicated recoveries, some have prolonged illness even after recovery from the acute illness (5-7). Identifying longer-term potential consequences and relationship with the acute illness is important for the management of patients, in particular, understanding how these interact and affect those already living with other conditions such as cardiovascular disease and cancer will be paramount.

However, very little is known about possible clinical sequelae that may persist after the resolution of acute infection. A recent longitudinal cohort of 143 patients followed after hospitalisation from COVID-19 in Italy, reported that 87% had at least one ongoing symptom, most (55%) with 3 or more symptoms at 60 day follow up, fatigue (53%), dyspnoea (43%), joint pain (27%) and chest pain (22%) being the most common. COVID-19 was associated with worsened quality of life among 44% of patients. (6) Prolonged course of illness has also been reported among people with mild COVID-19 who did not require hospitalisation (5, 7, 8).

Increasing evidence also suggests that infection with SARS-CoV-2 can cause neurological consequences, (2) including altered mental status, comprising encephalopathy or encephalitis and primary psychiatric diagnoses (9). While these symptoms arise acutely during the course of infection, less is known about the possible long-term consequences. Severely affected COVID-19 cases experience high levels of proinflammatory cytokines and acute respiratory dysfunction which often require assisted ventilation. These are known factors suggested to cause cognitive decline (2, 10).

Post-traumatic stress disorder (PTSD) and post-intensive care syndrome after intensive care unit (ICU) stay has been well documented previously (11-13). A systematic review of consequences after hospitalisation or ICU stay for severe acute respiratory infection (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) found sequelae up to 6 months after discharge. Common consequences besides impaired diffusing capacity for carbon monoxide and reduced exercise capacity were PTSD (39%), depression (33%) and anxiety (30%) (14). Additionally, serial CT scans post discharge after SARS-CoV showed a gradual healing of pulmonary injury, with pulmonary consequences lasting more than 6 months post discharge. (15)

Early indications suggest patients with COVID-19 will need even more psychological support than typical post-ICU patients because of higher levels of “survivors’ guilt” and PTSD (16). In addition, the characteristics of the initial cellular immune and antibody response to SARS-CoV-2 have not been fully

defined and it is not known if the immune responses generated by infection provides long-term protective immunity. Identifying multidisciplinary sequelae and complications through high quality, global studies throughout the course of COVID-19 is important for the acute and longer-term management of patients (4, 17).

The emerging data and anecdotal evidence of long-term recovery and persistent debilitating symptoms highlight the need for robust, standardised studies to assess the risk of and risk factors for COVID -19 sequelae. The purpose of this study is to establish a longitudinal cohort of patients with COVID -19 post-discharge to characterise the risk of long-term consequences over time in different populations globally. (18) The primary outcome is to characterise physical and psychosocial consequences in patients post-COVID- 19 infection. Secondary outcomes include estimating the risk of and risk factors for post-COVID-19 medical sequelae, psychosocial consequences and long-term outcomes. The results will inform strategies to prevent long term consequences; inform clinical management, interventional research, direct rehabilitation, and inform public health management to reduce overall morbidity and improve outcomes of COVID-19.

## **Methods and analysis**

This protocol and data collection surveys have been developed by the ISARIC COVID-19 global follow up working group and informed by a wide range of global stakeholders with expertise in clinical research, outbreak research, infectious disease, epidemiology, respiratory, critical care, rehabilitation, neurology, psychology, rheumatology, cardiology, oncology and public health medicine.(18)

### *Study design*

This is an international prospective, observational multi-site study to assess risk of and risk factors for longer term physical and psychosocial consequences of COVID-19.

The study conforms to research ethics standards and has been approved by research ethics boards in Colombia, Ghana, Italy, Norway and the UK and submitted for ethics approval in additional sites and

countries. All sites adopting the protocol are responsible for ensuring that they have local ethical approval in place.

### *Population and setting*

This protocol builds on the ISARIC/WHO COVID-19 clinical characterisation protocol (CCP) and associated data collection forms already in operation, the Core- and Rapid case report forms (CRFs).(19) These CRFs were developed to standardised clinical data collection on patients admitted with suspected or confirmed COVID-19, with clinical data on more than 88,463 individuals hospitalized with confirmed COVID-19 infection across 42 countries documented in a central database (as of 8 Oct. 2020). (20) These CRFs collect data on demographics, pre-existing comorbidities and risk factors, signs and symptoms experienced during the acute phase, and care and treatments received during hospitalization. (19) This acute phase data will be linked with the follow up data to inform analysis. A subset of these patients with confirmed COVID-19, will be followed up over time, documenting data on longer term consequences using the Tier 1 follow up data collection surveys.(18) There is no limit on the number of sites or countries taking part.

New clinical sites are invited to take part in this global collaborative effort and use these open-access tools. New sites can complete the Core- or RAPID- CRFs prospectively or retrospectively (Fig.1). Sites adopting the protocol and tools for collaborative or independent studies are responsible for ensuring local regulatory and ethical approvals are in place as appropriate.

Specific inclusion and exclusion criteria are as follows:

### *Inclusion criteria*

- People aged 16 years and older
- Laboratory or physician confirmed COVID -19
- At least 1 month post- discharge from hospital or health centre
- Person (or family member/carer for patients who lack capacity) consent to participate

### *Inclusion of vulnerable participants*

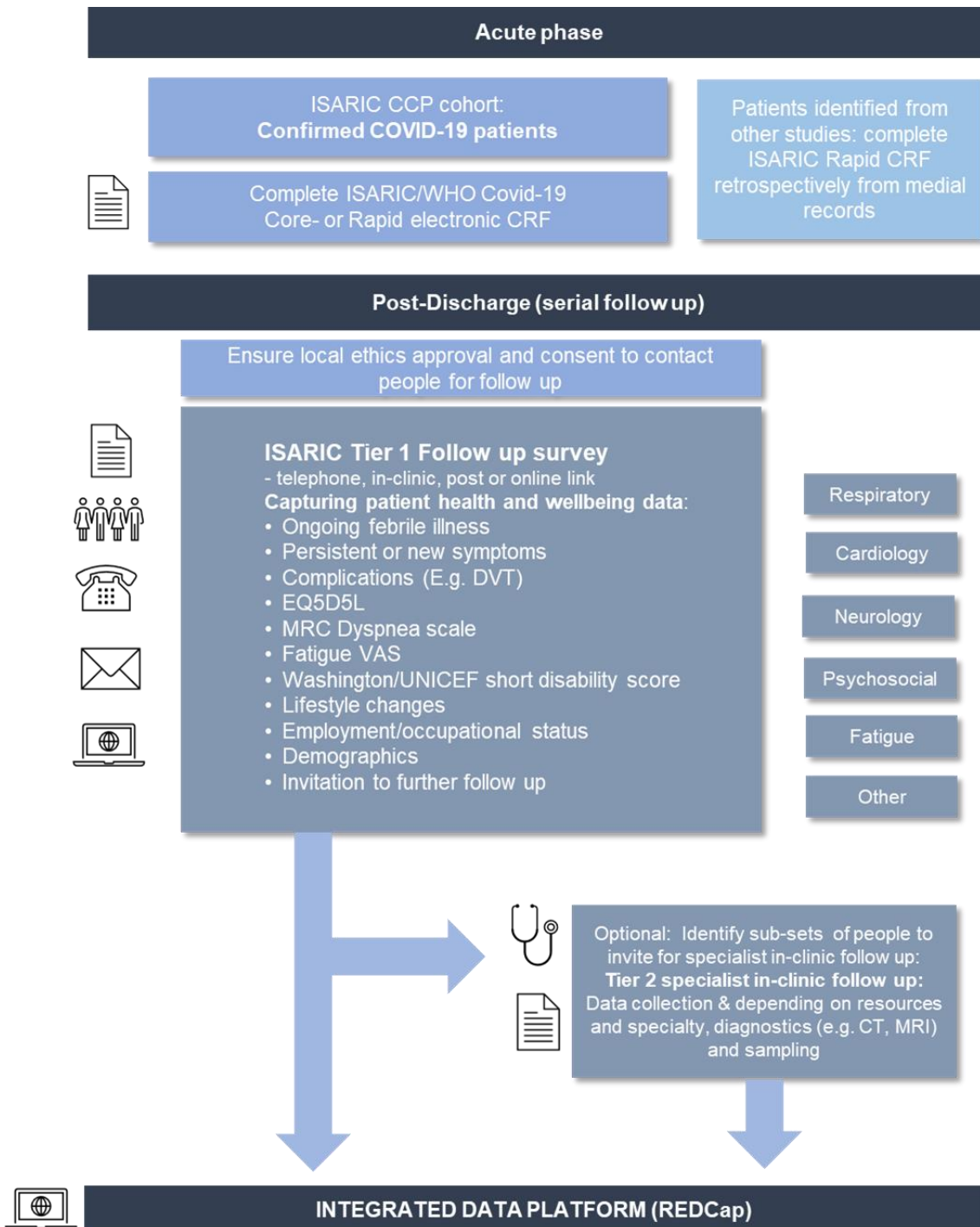
The data collection surveys and validated tools are developed for anyone who fit the inclusion criteria, including pregnant women, elderly and those who are immunosuppressed. An aligned study protocol and survey will be developed for following up children.

### *Outcomes and Procedure*

The follow up protocol and survey are designed to be flexible in a tiered approach to be adapted depending on local resources and research needs. The Tier 1 survey is designed to enable patient self-assessment to facilitate distribution to all patients that fit the inclusion criteria, using a range of methods via post, an online link for self-completion or via telephone or in-clinic completion. A combination of methods can be used to reach as a wide population as possible and depending on site resources. The survey can be adapted and adopted as a standardised data collection tool as part of other studies e.g. in combination with sampling and/or diagnostic methods for further analysis (Tier 2) (Figure 1).



Figure 1. ISARIC’s adaptable Covid-19 Follow-Up Protocol framework



**Abbreviations:** ISARIC: International Severe Acute Respiratory and emerging Infection Consortium, MRC: The Medical Research Council, VAS: Visual analogues scale, WHO: World Health Organisation

### *Serial follow up*

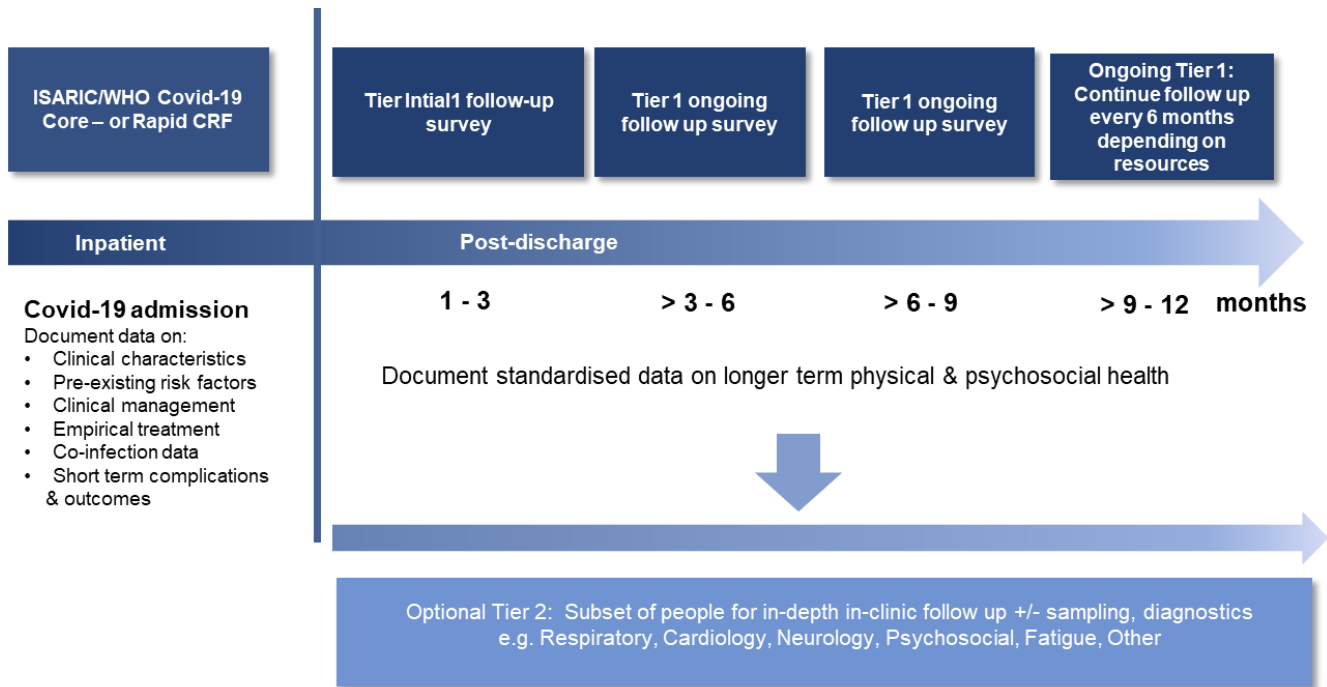
The aim is to follow up patients serially over time, for as long as there is a need and resources at regular intervals. The Tier 1 initial survey will be used at the initial follow up timepoint (at 1 to 3 months post discharge). The Tier 1 ongoing survey will be used at subsequent follow up time points every 3 to 6 months depending on resources (Fig. 2). To facilitate combined analysis the time frames in Figure 2 are recommended. These can be adapted depending on local resources and needs. For sites that have capacity, the Tier 1 form can be used to identify people for in clinic follow up or subset of people for serial follow up. By being designed for patient self-completion to be administered via an online link or as a paper form, it allows wide distribution at low resource need. It can also be completed via in-clinic or telephone assessments during check-ups or for patients that are still hospitalised. The module will collect data on demographics, hospital stay and re-admissions, all-cause and cause specific mortality (after the initial index event), specific consequences including; deep vein thrombosis (DVT), pulmonary embolism, recent febrile illness, new or persistent symptoms, quality of life (measured by EQ-5D-5L), dyspnoea (assessed using MRC dyspnoea scale), difficulties in functioning (UN/Washington disability score), lifestyle and socioeconomic data.(18) Medical records will be used to assess if a person is deceased before each follow up time point, and documented in the database. The ISARIC collaborative follow up study is registered with EuroQol. Sites who wish to adopt the survey for independent studies, outside of the ISARIC collaboration need to register to use EQ-5D-5L tool with EuroQol.

### *Sub-studies*

The Tier 1 follow up module can be used to identify sub-sets of patients experiencing specific symptomatology or syndromes for further follow up. By using a tiered approach, additional specialist modules can be added for more complex follow up of emerging consequences in a flexible, adaptable way, of a subset of patients, and combined with sampling and diagnostics (Figure 1 and 2).

**Figure 2. Schematic overview of the follow up data time-frames**

Serial follow up will continue beyond 12 months at 6 months' interval for up to 3 years depending on resources.



**Abbreviations:** ISARIC: International Severe Acute Respiratory and emerging Infection Consortium, WHO: World Health Organisation

### Biological samples

The Tier 1 surveys can be used on its own for data collection, or in combination with sampling (e.g. respiratory samples, serum, blood, stool, urine), for immunology, pathophysiology, genomics or other studies (16). This protocol builds on the ISARIC/WHO Clinical Characterisation Protocol (CCP) which includes an adaptable research sample schedule for sites with resources for adding optional research sampling and analysis (19, 21). The CCP is designed for any severe or potentially severe acute infection of public health interest, such as COVID-19. It is a standardized protocol for data and biological samples to be collected rapidly in a globally harmonised manner.(21, 22) The CCP can be used for the rapid, coordinated clinical investigation of confirmed cases of COVID-19. It is also designed in a tiered approach to be adapted depending on resources and includes different levels of sampling schedules

(acute phase and follow up) that can be adapted depending on resources, to be combined with patient data collection using the acute phase CRFs and the follow up CRF. (18, 19)

### *Outcomes*

The primary outcome of this study is to characterise physical and psychosocial consequences in patients post-acute COVID- 19. Secondary outcomes include estimating the risk of and risk factors for post-COVID- 19 medical sequelae, psychosocial consequences and post-COVID-19 mortality.

### *Data collection and entry*

A standardised COVID-19 follow up survey aimed for global settings was developed through a series of virtual working group meetings and e-mail iterations. The survey was piloted on patients in four settings in three countries and feedback incorporated into the final form. This Tier 1 follow up survey is designed for patient self-assessment, via online link or paper form, or to be completed during in-clinic or telephone follow-up appointment (Fig.1). (18) The CRF is available open access on the ISARIC website and as an electronic form on the ISARIC hosted REDCap database. (18) The survey can be distributed directly to patients via an online link.

### *Statistical analysis plan*

Using the data, we will test for differences in outcomes across important demographic groups (age categories, sex, ethnicity, socioeconomic deprivation, comorbidities), specific exposures (severe COVID-19, critical care admission, ventilation) and initial clinical sequelae (complications on their index admission for COVID-19). We plan to use this platform to conduct timely analyses which coincide with public health or scientific need. Given these requirements, new questions we have not specified within this protocol may arise. Where this occurs, we will develop analysis plans prior to undertaking analyses, which will be made available on request. The data collected through the follow up module will be linked with data on demographics, comorbidities, clinical characteristics, care and treatments collected using the ISARIC/WHO Core- or RAPID COVID-19 CR.(19)

Fields contained within the data collection forms will be combined and if an area of interest is found, the maximal amount of data will be used to investigate this to maintain sample size and power. The plan below presents our guiding statistical framework. Analyses will be developed concurrently with data collection using statistical coding script. At appropriate time intervals, scripts will be run to produce analyses at these timepoints over the course of the project.

As COVID-19 is a new disease, there are no systematically collected long-term data to base formal sample size calculations upon. Therefore, we intend to recruit as many patients as possible. Through the network established already, this is anticipated to be very large. Therefore, as a minimum calculation, to perform logistic regression, we will use at least 10 events for each variable included in the regression. For a regression containing 10 explanatory variables, 100 events would be included within the model for each variable. Assuming a sequelae rate of at least 20%, we would need at least 500 patients which should be adequately achieved. As the field is rapidly evolving, the analyses are likely to change.

Entered data will be summarised first by using simple summary statistics. Categorical data will be explored using frequencies and percentages, with differences in disease severity and treatment groups tested for using Chi-square tests or Fisher's exact test where cell counts are under five. For continuous data, distribution will be established using histograms and density plots. Data that are normally distributed will be summarised using group mean averages and standard deviation as a measure of central tendency. For non-parametric data, the median average will be used and presented alongside 25<sup>th</sup> and 75<sup>th</sup> centiles. Differences in normally distributed continuous data will be tested using Welch's two sample t-tests for 2 group data and ANOVA for three or more groups. Mann-Whitney U will be used to compare differences across two groups or Kruskal-Wallis tests for three or more groups, where data follow a non-parametric distribution.

Outcomes will be expressed in three ways; 1) binary event data (for presence or absence of outcome of interest), 2) change over time (for continuous or ordinal data), or as 3) time to event data (for patients

with serial measurements). We will calculate changes over time across symptom and outcome variables and use these changes over time to compare the effect of treatments or exposures on these outcomes. Time to event data will be captured for those who complete serial assessment forms. These data will be presented as Kaplan-Meier plots and differences tested for using log-rank tests. Competing risks (including death) will be accounted for using censoring.

To address the main aim of characterising the middle to long-term impact of COVID-19 on physical and mental health, we will first provide simple summaries of incidence and second, characterise which patients are at risk of developing these. To identify which patients are likely to develop persistent complications, functional impairment or reduced quality of life, we will use multilevel models to adjust for potential confounders. Level I fixed effects will include patient-level explanatory variables (i.e. age, sex) and level II or III random effects will include site and country in the case where research questions require differences in country to be accounted for. Explanatory variables will be entered into models since clinical plausibility and final model selection guided by maximisation of the adjusted  $R^2$  value and minimisation of the Akaike information criterion (AIC) or Bayesian information criterion (BIC). For binary event data, multilevel logistic regression will be used, and estimates presented as odds ratios alongside the corresponding 95% confidence interval. For continuous data, linear or generalised linear regression will be used, and estimates presented as model coefficients, with 95% confidence intervals. Finally, time to event data will be presented as survival probability or hazard ratios, with 95% confidence intervals.

Statistical significance will be taken at the level of  $P < 0.05$  *a-priori*. Analyses will be conducted in secure R (R Foundation for Statistical Computing, Vienna, AUT) or STATA (StataCorp LLC, TX, USA) environments.

#### *Data sharing*

Sites who wish to utilise ISARIC's COVID-19 data management and hosting support can email [ncov@isaric.org](mailto:ncov@isaric.org) to gain access to a secure data capture and management system. All systems are free

to use and supported by ISARIC data management specialists. Sites who submit data to ISARIC will sign a Terms of Submission, enabling use of the data in collaborative analysis by ISARIC partners.

### **Ethics and dissemination**

Since the emergence of SARS-CoV-2 in December 2019, there has been a considerable global effort to characterise the virus and clinical course of disease. This has included identification of the virus, rapid design and development of diagnostics, host cell receptor identification, and insights into early epidemiological and clinical parameters. However, very little is known about possible clinical sequelae that may persist after resolution of the acute COVID-19. Emerging data indicates impact of COVID-19 infection on not only the respiratory system but also the kidneys, liver, neurological, psychological and multisystem inflammatory syndrome (2, 4, 9, 23). Moreover, with increasing reports of long-term consequences, there is an urgent need to characterise the risk of short and chronic consequences and risk factors and biomarkers for patients at risk of sequelae, to inform preventative and rehabilitation strategies.

The assessment of risk factors for longer term consequences requires a longitudinal study linked to data on pre-existing conditions and patient data and care received during the acute phase. A subset of patients included in the ISARIC/WHO clinical characterisation protocol have provided consent to be contacted for follow up. Additionally, sites taking part in the global follow up study will apply for consent to follow up patients confirmed with COVID-19, following the local ethical committee procedures. These standardised protocols and tools will serve as a standardised template that can be modified as appropriate and needed at each site. With this study we aim to characterise the risk of long-term consequences over time in patients following a diagnosis of COVID-19. We will collect data on a wide range of outcomes including hospital stay and re-admissions, all-cause and cause specific mortality (after the initial index event), new or persistent symptoms and complications, e.g. DVT, pulmonary embolism, recent febrile illness, new, persistent symptoms, EQ-5D-5L, MRC dyspnoea scale,

UN/Washington disability score, lifestyle and employment data. Data from combined analysis will be disseminated through the ISARIC website and in open-access publications under group authorship. The follow up module is developed as an open-access, flexible tool to be adopted and adapted as appropriate depending on need and resources by any site globally interested in following up patients with COVID-19 over time, to facilitate standardized data collection globally and combined analysis. The outcomes of this study will inform strategies to prevent risk of consequences; clinical management, rehabilitation, and public health management, to reduce morbidity and improve outcomes. By standardising data collection, and providing open-access, adaptable tools, focused on key data variables, it can optimize data quality and reduce the burden of research on staff, while collecting the most relevant information to inform clinical care guidelines and public health. The Tier 1 follow up survey is available in English, Italian, Portuguese, Russian and Spanish.(18) The survey will be translations into additional languages as required.

#### *Data statement*

ISARIC stands by the principles of data sharing in public health emergencies. ISARIC supported studies will share quality data in a timely, valid, and governed manner to inform public health policy and benefit patient care. The ISARIC-hosted data platform enables rapid and harmonised operationalisation of data collection to a secure database (24). Ownership and control of the data entered are retained by those who enter the data. Sites can contribute data to combined analysis upon permission. Technical appendix, statistical code and datasets are available from <https://isaric.org/document/covid-19-data-management-hosting/> or by contacting: [ncov@isaric.org](mailto:ncov@isaric.org). Research outcomes will be disseminated via the ISARIC website and published in peer-reviewed scientific journals under a collaborative group authorship. The data contributors will share the outcome results with key stakeholders to inform public health response, policy development and implementation. To efficiently make findings from this project visible and accessible to a wide range of stakeholders as well as to networks of individuals and institutions, we will utilise social media, including the ISARIC and partner institution's websites. The consortium will manage a page dedicated to this project that will incorporate all the tools available. The



webpage will provide not only updates on the progress of the project and component activities and events, but also information on research.

This follow up study is developed as an open-access tool to be adopted as appropriate by any site interested in following up patients with COVID-19 over time, to facilitate standardised data collection globally to enable combined analysis. New sites globally are invited to join the study at any time. The outcomes of this study will inform strategies to prevent risk of consequences; clinical management, rehabilitation and public health management needs to reduce morbidity and improve outcomes. We invite hospitals and healthcare centres globally to collaborate and take part in the study.

### **Acknowledgments**

We would like to thank the ISARIC global clinical characterisation group, ISARIC4C and all the clinicians, nurses and researchers contributing COVID-19 clinical patient data, which will be linked with the follow up data, and all the patients that have consented to be followed up. We would like to acknowledge WHO, whose working groups contributed to development of the CCP and associated tools. Moreover, everyone at the ISARIC Global Support Centre, Anneli Sandström and Tova Strong.

**Ethical approval:** Ethical approval has been given by the Universidad de La Sabana's IRB (US-MED-504), Colombia; Ghana Health Service Ethics Review Committee and at the Comitato Etico di Brescia, Italy, South-Eastern Norway Regional Health Authority, Norway (Ref 106624). In the UK, for day – 28 follow up as part of the UK CCP approved by the South Central - Oxford C Research Ethics Committee in England (Ref 13/SC/0149) and the Scotland A Research Ethics Committee (Ref 20/SS/0028). The protocol is under review at the Comitato Etico per la sperimentazione Clinica delle Province di Verona e Rovigo, Italy, the Sechenov University Ethics Committee, Moscow, Russian Federation and the University of Witwatersrand Human Research Ethics Committee (Medical), Johannesburg, South Africa

and is being submitted to the National Ethics Committee (CONEP), Rio de Janeiro, Brazil, and in Freetown, Sierra Leone. Sites interested in adopting the protocol as it is or in an adapted version are responsible for ensuring that local sponsorship and ethical approvals in place as appropriate.

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