Interventions for preventing and treating COVID-19: protocol for a living mapping of research and a living systematic review

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ABSTRACT

Objective: To provide researchers and decision-makers with a detailed and up-to date mapping of all registered randomized controlled trials evaluating interventions for preventing and treating COVID-19 and to develop and maintain a living evidence synthesis of randomized trials and quasi-experimental studies (i.e., interrupted time-series studies and non-randomized studies using causal inference analysis) evaluating these interventions.

Design: We will perform a living mapping of registered randomized trials and a living systematic review with pairwise meta-analyses and when possible, network meta-analyses focusing on two main questions: 1) the effectiveness of preventive interventions for COVID-19 and 2) the effectiveness of treatment interventions for COVID-19. We will evaluate the impact of these treatments considering the severity of the disease (i.e., mild, moderate, severe and critical diseases).

Methods: We will systematically search the World Health Organization (WHO) International Clinical Trials Registry Platform and electronic bibliographic databases (PubMed, MedRχiv, Chinaxiv, China National Knowledge Infrastructure database) to identify all randomized controlled trials and quasi-experimental studies evaluating the effectiveness of interventions for preventing the spread of COVID-19 (e.g., vaccination, prophylactic interventions, personal protective equipment, models of practice and organization of care, etc.) or treating COVID-19 (e.g., specific therapeutic agents for COVID-19 such as anti-infectious agents, specific immunomodulators, non-specific immunomodulators, supportive management for patients admitted to the intensive care unit, general treatments for viral infection, models of practice and organization of care etc.). Screening, data extraction and risk of bias assessment will be performed in duplicate. The living systematic review will be updated at least once a week if new evidence is available. We will also systematically contact authors of trials with results available to request individual- participant data.

Conclusion: Our work will provide an updated synthesis of available evidence. Our results will be essential for healthcare providers, researchers, the public and other decision-makers for preventing COVID-19, caring for patients with COVID-19, planning future trials and managing the pandemic on a public health level. Our analyses will be available publicly on a website that will be updated regularly.

1 BACKGROUND

In December 2019, a novel coronavirus outbreak was documented in Wuhan, Hubei Province, China. Over the first 6 weeks of the new decade, this coronavirus, known as SARS-CoV-2, spread from China to several countries of the world, and WHO declared COVID-19 a pandemic on March 11, 2020.

The estimated number of people who will be infected with SARS-CoV-2 by one contagious person — the baseline reproduction number, R0 — is estimated at 2.4 to 3.3[1]. In other words, with an R0 of about 3, about two-thirds of all transmissions must be prevented to bring the epidemic under control. At the time of writing, the cumulative incidence of COVID-19 cases is following an almost exponential trend in most European countries and the United States[2].

COVID-19 can cause various clinical manifestations from non-specific flu-like symptoms (fever, dry cough, fatigue) to severe hypoxemia, multiorgan failure, and death. Severe forms usually manifest a week after the onset of symptoms. Most people with COVID-19 show only mild or uncomplicated illness, but approximately 14% exhibit severe disease that requires hospitalization and oxygen support; 5% require admission to an intensive care unit (ICU)[3]. Although frail older patients are at higher risk, young and otherwise healthy patients can have severe forms as well[4].

To address this pandemic, researchers are working to accelerate the development of diagnostic tests, preventive interventions and therapeutic interventions. Many randomized trials have been established to evaluate candidate therapeutic agents that may effectively reduce symptoms and avoid deaths. This emerging situation requires the optimal planning and conduct of trials as well as strategies for the appropriate translation of research into practice. Therefore, decision-makers and researchers urgently need a complete, high-quality and up-to-date synthesis of data from all ongoing research studies as soon as they are available. To this end, we will perform 1) a living mapping of registered randomized trials and 2) a living systematic review and network meta-analysis of randomized trials and quasi-

experimental studies (i.e., interrupted time-series studies and non-randomized studies using causal inference analysis).

Our living mapping will allow us to monitor in real-time new evidence that becomes available for treating and preventing COVID-19. In this way, we will also be able to identify gaps and deficiencies within the existing evidence body early to help identify and prioritize future research efforts. Gathering any available piece of information as soon as it becomes available will enable the conduct of a living systematic review with pairwise comparisons and network meta-analyses (NMAs) as a next step.

As part of the methodological process of living systematic reviews, we will continuously (i.e., every day) collect and critically appraise results from all available randomized trials and quasi- experimental studies addressing specific clinical outcomes related to COVID-19. We will synthesize the available study results using pairwise meta-analyses and when possible and appropriate, NMAs. The interventions and the research questions considered will evolve over time and will be guided by users' needs.

We will consider the following specific research areas/topics/questions:

A) The effectiveness of interventions for preventing the spread of COVID-19

We will particularly consider the following preventive interventions aimed at reducing the secondary transmission of COVID-19 in healthcare providers and the community, particularly vaccination, prophylactic interventions, personal protective equipment, models of practice and organization of care (e.g., checklists, training, dedicated staff to ensure compliance to preventive interventions, organization of patient transportation), and movement control strategies.

B) The effectiveness of interventions for treating COVID-19

The following interventions will be considered:

1. Specific therapeutic agents for COVID-19 such as anti-infectious agents, specific immunomodulators, non-specific immunomodulators
2. Supportive interventions for patients admitted to the ICU such as high-flow nasal canula, non-invasive ventilation, protective mechanical ventilation and extracorporeal membrane oxygenation (ECMO)
3. General treatments for viral infection such as vitamin C, zinc, selenium etc.
4. Models of practice and organization of care (e.g., checklists, training, dedicated staff to ensure compliance with preventive interventions, organization of patient transportation, etc.)

We will consider both the treatments and treatment combinations. We will evaluate the impact of these treatments regimens considering the severity of the disease (i.e., mild, moderate, severe and critical diseases).

The different treatment regimens and preventive interventions considered in this living mapping and systematic review will evolve over time as the research field is continuously evolving.

2 METHODS

The process is described in the figure.

2.1 Criteria for considering studies for this review

2.1.1 Types of studies

We will include randomized controlled trials and quasi- experimental studies i.e., interrupted time-series studies and non-randomized studies using causal inference analysis (e.g., propensity score, instrumental variables, inverse probability weighting, etc.)[7].

We will include in the synthesis only quasi-experimental studies at low risk of bias as evaluated by Cochrane Risk of Bias tool for non-randomized studies of interventions (i.e., ROBINS[5]). RCTs and quasi-experimental studies will only be combined in the same analysis after careful examination of the risk for violating the homogeneity and transitivity assumptions.

Systematic review and meta-analyses of COVID-19 prevention/treatments will be retrieved and the references will be screened.

Early-phase clinical trials, single arm trials, observational studies and modelling studies of interventions for COVID-19 will be identified and cited on a website to inform the research community but will not be included in the review.

We will exclude studies about prognosis, systematic reviews and meta-analyses, diagnostic test accuracy studies, and modelling studies.

2.1.2 Types of participants

For each research question, we will consider different participants.

For preventive interventions, we will consider

- The local community
- Healthcare providers

For treatment interventions, we will consider

- Suspected, probable or confirmed COVID-19 patients (see classification in appendix 1[10]).

We will distinguish patients according to the severity of the disease (i.e., mild, moderate, severe and critical diseases).

2.1.3 Types of interventions

A) The effectiveness of interventions for preventing SARS-CoV-2

We will particularly consider the following preventive interventions aimed at reducing human-to-human transmission of COVID-19 in healthcare and in the community:

- vaccination
- prophylactic interventions, such as pharmacologic treatment provided to people exposed to COVID-19 patients
- personal protective equipment
- models of practice and organization of care (e.g., checklist in ICU, training, dedicated staff to ensure compliance with preventive interventions, organization of patients' transportation, etc.)
- movement control strategies (e.g., self-isolation, quarantine, enforced lockdown).

B) The effectiveness of interventions for treating COVID-19

1. Evaluation of the effectiveness of specific therapeutic agents for COVID-19.

   Specific therapeutic agents will consist of

   a. anti-infectious agents including antiviral treatments such as remdesivir, lopinavir-ritonavir, oseltamivir, favipiravir and umifenovir; chloroquine and hydroxychloroquine; azithromycin, etc.
   b. specific immunomodulators such as interferon alpha, interferon beta, nivolumab, tocilizumab, etc.
   c. non-specific immunomodulators such as corticosteroids, polyclonal antibodies, convalescent plasma, etc.

2. Evaluation of the effectiveness of supportive treatments for patients admitted to the ICU, such as high-flow nasal canula, non-invasive ventilation, protective mechanical ventilation, ECMO (Extracorporeal Membrane Oxygenation).
3. Evaluation of the effectiveness of general treatments for viral infection such as vitamin C, zinc, selenium etc.
4. Evaluation of the effectiveness of models of practice and organization of care

C) The effectiveness of post-discharge interventions

1. Rehabilitation
2. Other interventions

We will exclude studies evaluating Traditional Chinese Medicine, decontamination methods, studies not performed on human (mannequin) or in real condition (e.g., simulation).

Appendix 2 provides a list of interventions currently evaluated in trials registered on the WHO International Clinical Trials Registry Platform.

We will evaluate the effectiveness of these treatments considering the severity of the disease and comorbidities in subgroup analysis (ref WHO[4,11]). Particularly we will consider the following:

- **Mild disease** — clinical symptoms are mild with no sign of pneumonia on imaging
- **Moderate disease —** fever and respiratory symptoms with radiological findings of pneumonia and requiring oxygen (3 L/min>oxygen <5 L/min)
- **Severe disease —** cases meeting any of the following criteria:
    - respiratory distress (≧ 30 breaths/min)
    - oxygen saturation ≤ 93% at rest in ambient air or oxygen saturation ≤97% with $O_2 \geq 5$ L/min.
    - PaO_2/FiO_2 ≦ 300 mmHg (l mmHg=0.133 kPa). PaO_2/FiO_2 in high-altitude areas (> 1,000 m above sea level) will be corrected by the following formula: PaO2/FiO2 x [atmospheric pressure (mmHg)/760]
    - chest imaging showing obvious lesion progression within 24-48 hr
- **Critical disease —** cases meeting any of the following criteria
    - respiratory failure and requiring mechanical ventilation
    - shock
    - other organ failure that requires ICU care

The treatments and preventive interventions considered in this living mapping and systematic review will likely expand over time to take into account new emerging management options and combination regimens.

Interventions will be included in the same NMA only when we anticipate that any patient who meets the pre-defined inclusion criteria would, in principle, be equally likely to be randomized to any of the interventions within a network. If additional interventions not listed here will be identified, they will

be included in our review in our analyses as long as their inclusion will not be likely to violate the underlying assumptions.

2.2 Outcome measures

We based our outcome selection on the CORE outcome sets developed by the WHO[12] and on the meta-COS for research in COVID-19 hospitalized patients identified through the COMET initiative (http://www.comet-initiative.org/Studies/Details/1538).

The outcomes considered will evolve over time to take into account the new CORE outcome set being developed by the COMET initiative (http://www.comet-initiative.org/Studies/Details/1538) and any other important outcome that may arise over time.
On April 27, we updated our outcomes. Particularly, we deleted outcomes that could be in competition with death (e.g., ventilation) or other events and use now composite outcomes (e.g., Incidence of level 7 or above on the WHO Clinical Progression Score).

We will consider the following **primary outcomes**:

- Prevention of COVID-19
    1. Incidence of symptomatic or asymptomatic secondary COVID-19

- Treatment of COVID-19 patients
    1. Incidence Viral Negative Conversion (D3, D7)
    2. Clinical improvement (D7 / D14 / D28 / D60 / D90). As the definition for clinical improvement can vary, we will systematically collect how it was defined in each study.

3. WHO Clinical Progression Score level 5 or above (i.e., low flow oxygen by mask/nasal prongs OR NIV/High Flow 02 OR mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death) (D7 / D14 / D28 / D60 / D90)
4. WHO Clinical Progression Score level 6 or above (i.e., NIV/High Flow 02 OR mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death) (D7 / D14 / D28 / D60 / D90)
5. WHO Clinical Progression Score level 7 or above (i.e., mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death (D7 / D14 / D28 / D60 / D90)
6. All-cause mortality (D7 / D14 / D28 / D60 / D90)

We will consider the following **secondary outcomes**:

- Treatment of COVID-19
    1. Time to 2019-nCoV RT-PCR negativity
    2. Time to clinical improvement
    3. Length of Stay in Hospital
    4. Length of Stay in ICU
    5. Duration of invasive mechanical ventilation
    6. Time to death

We will consider the following **safety outcomes**:

1. Incidence of serious adverse events (SAEs)
2. Incidence of AEs

Other scales than the WHO progression scale can be used in trials. Consequently, we will systematically determine the correspondence between the different scales. An example is reported in appendix 4.

For the analysis, we will group some time points (e.g., D7-14; D14-28). Further, when the outcomes are assessed at different time points than the one selected, we will choose the closest (e.g., D15 for D14). We will also consider a joint analysis of multiple time points when sufficient data will be available[13].

2.3 Search strategy and study selection

For this review, it is crucial that we identify relevant results as rapidly as possible. Therefore, we will target databases for which data from clinical trials on COVID-19 can easily be retrieved and use strategies that maximize specificity.

The search strategy was developed with Robin Featherstone, Information Specialist, at Cochrane Editorial & Methods Department. The search strategy will be updated and modified to rely on the Cochrane living registry of available COVID-19 studies.

We recognize that information sources are being developed rapidly in the current situation. We will add/modify our evidence sources based on the availability of new eligible resources. Currency, usability and the credibility of new information sources will all be considered when selecting sources to integrate into our search strategy.

In collaboration with the WHO Collaborative Centre for Guideline Implementation and Knowledge Translation and Chinese GRADE Centre (Lanzhou University, China), the Chinese literature is being extensively searched (appendix 3).

2.3.1. Priority sources

- The **World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP**, https://www.who.int/ictrp/en/), to identify ongoing and completed clinical trials on COVID-19. We will use the List By Health Topic: 2019-nCoV / COVID-19 filter and retrieve all studies identified.

- **PubMed** (https://pubmed.ncbi.nlm.nih.gov)

We will use the following search to identify randomized trials:

Search	Query
#9	#8 Filters: **Publication date from 2020/01/01**
#8	Search: **#4 AND #7**
#7	Search: **#5 NOT #6**
#6	Search: **animals[mh] NOT humans[mh]**
#5	Search: **randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]**
#4	Search: **#1 OR #2 OR #3**
#3	Search: **severe acute respiratory syndrome coronavirus 2[Supplementary Concept]**
#2	Search: **COVID-19[Supplementary Concept]**
#1	Search: **"2019 nCoV"[tiab] OR 2019nCoV[tiab] OR "2019 novel coronavirus"[tiab] OR "COVID 19"[tiab] OR COVID19[tiab] OR "new coronavirus"[tiab] OR "novel coronavirus"[tiab] OR "SARS CoV-2"[tiab] OR (Wuhan[tiab] AND coronavirus[tiab])**

To identify observational studies, we will use the following search:

Search	Query
#9	#8 Filters: **Publication date from 2020/01/01**
#8	Search: **#6 NOT #7**
#7	Search: **animals[mh] NOT humans[mh]**
#6	Search: **#4 NOT #5**
#5	Search: **editorial[pt] OR comment[pt] OR letter[pt] OR newspaper article[pt]**
#4	Search: **#1 OR #2 OR #3**
#3	Search: **severe acute respiratory syndrome coronavirus 2[Supplementary Concept]**
#2	Search: **COVID-19[Supplementary Concept]**
#1	Search: **"2019 nCoV"[tiab] OR 2019nCoV[tiab] OR "2019 novel coronavirus"[tiab] OR "COVID 19"[tiab] OR COVID19[tiab] OR "new coronavirus"[tiab] OR "novel coronavirus"[tiab] OR "SARS CoV-2"[tiab] OR (Wuhan[tiab] AND coronavirus[tiab])**

We will update the search strategies in PubMed to incorporate the names of the drugs we identify in our work when appropriate.

- **CNKI (**China National Knowledge Infrastructure, https://www.cnki.net/) **database** and (http://journal.yiigle.com/) using the following search Strategy:
    - #1 “2019冠状病毒”
    - #2 “新型冠状病毒”
    - #3 “新冠肺炎”
    - #4 “武汉2019”
    - #5 “武汉病毒“

- #6 “武汉肺炎”
- #7 “2019-nCoV”
- #8 “SARS-CoV-2”
- #9 “Novel coronavirus”
- #10 “nCoV”
- #11 “Emerging Coronavirus”
- #12 “new coronavirus”
- #13 “COVID-19”
- #14 “coronavirus”
- #15 OR/#1-#14

- **MedRχiv** (https://www.medrxiv.org): MedRχiv is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in the medical, clinical, and related health sciences. A curated list of records on COVID-19 and SARS-CoV-2 is available at https://connect.biorxiv.org/relate/content/181. Note that this list also includes sources listed in bioRχiv, but we will only screen the sources published on MedRχiv (i.e., titles in blue rather than red).

- **Chinaxiv** (http://chinaxiv.org/) Chinaxiv is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in Chinese.

2.3.2. Secondary sources

These sources will be searched as a quality control, and if no studies are identified over 8 weeks, these sources will be abandoned.

- **LitCOVID** (https://www.ncbi.nlm.nih.gov/research/coronavirus/), a curated database that tracks scientific evidence on COVID-19 published in PubMed. The hub is updated daily and studies are categorized by domain (e.g., "transmission" or "treatment" (https://www.nature.com/articles/d41586-020-00694-1). We will screen studies listed under "treatment".
- **WHO database of publications on coronavirus disease** (COVID-19) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov)
- **ClinicalTrials.gov** (https://clinicaltrials.gov/ct2/home), using the term "COVID-19" to check all trials listed on the WHO platform
- **The EU clinical trial register** (https://www.clinicaltrialsregister.eu/) using the term "COVID-19" to check all trials listed on the WHO platform
- **The Cochrane COVID-19 Study register** (https://covid-19.cochrane.org/)
- We will regularly contact investigators of ongoing studies to update the status of their study and obtain results.
- We will screen other sources such as the EPPI-Centre living map of evidence (http://eppi.ioe.ac.uk/COVID19_MAP/COVID_map_v5.html), Meta-evidence developed by Campbell UK & Ireland (http://meta-evidence.co.uk/).

We will use an Excel spreadsheet to document search dates and numbers of hits identified. Screening will be done in duplicate.

2.4 Data extraction

Two reviewers will independently read each preprint, publication, protocol, or other study report available; evaluate the completeness of the data availability; and assess the risk of bias. We will design and use a structured data extraction form to ensure consistency of information. Information extracted will include study characteristics (such as first author, publication year and journal), number of participants randomised, patient characteristics (such as mild or severe clinical presentation), intervention details (such as class and type of treatments), outcome measures, and risk of bias assessment.

For dichotomous outcomes, we will extract the number of events and number of total participants in each study arm. For continuous outcomes, we will extract means, standard deviations (SDs) and number of total participants per study arm. When SDs are not available but standard errors, t-statistics or p-values are reported, we will extract these and transform to SDs when possible. For time-to-event outcomes, we will extract hazard rations (HR) and standard errors (SE). When these are not provided, we will attempt to obtain them using the tools provided in Tierney et al.[14]

For missing outcome data, we will extract the number of participants who dropped out before the completion of the study and how missing outcome data were handled by the study authors. We will assess the appropriateness of any imputation methods used to account for early dropouts in our risk of bias assessments. To assess the potential impact of missing outcome data on the results, we will conduct sensitivity analyses, making different assumptions.

All data will be extracted in duplicate, with consensus in case of disagreement.

We will systematically contact authors and ask them to supply 1) information that could not be retrieved from the available study reports and 2) individual-participant data (IPD). These data will be curated and stored. In the presence of IPD, we will re-analyse the outcomes. Furthermore, if possible,

we will conduct IPD NMAs. If acquiring IPD for some of the studies will be deemed feasible, a specific protocol describing the methods to perform IPD meta-analyses and NMA will be prepared.

2.5 Risk of bias assessment

The risk of bias of each study will be assessed with the Cochrane risk of bias tool RoB 2 for randomized controlled trials and ROBINS-I for non-randomized studies of interventions [8,9].

The Cochrane risk of bias tool RoB 2 is structured into 5 domains: 1) risk of bias arising from the randomization process, 2) risk of bias due to deviations from intended interventions, 3) risk of bias due to missing outcome data, 4) risk of bias in measurement of the outcome, 5) risk of bias in selection of the reported result. Within each domain, a series of 'signaling questions' elicit information relevant to risk of bias risk of bias assessment. The response options to the signaling questions are: “Yes”; “Probably yes”; “Probably no”; “No”; and “No information”. A risk of bias judgement arising from each domain is generated by an algorithm, based on answers to the signaling questions. Judgement can be 'Low', ‘Some concerns’ or 'High' risk of bias. Overall risk of bias will be considered as “low risk of bias” if all domains are at ‘low risk’; “some concerns” if at least one domain is ‘some concern’ and no domain ‘high risk of bias’; and “high risk of bias” if there is at least one domain ‘high risk’, or several domains with ‘some concerns’. In the context of this protocol, we are interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (i.e., the ‘intention-to-treat effect’).

The ROBINS-I tool is a risk of bias tool to assess risk of bias in non-randomized studies of interventions. When using the tool, we will consider the the effect of interest will typically be

Assignment to intervention at baseline (start of follow up), regardless of the extent to which the intervention was received during the follow-up (sometimes referred to as the “intention-to-treat” effect); The tool is structured in 7 domains: 1) Bias due to confounding; 2) Bias in selection of participants into the study; 3) Bias in classification of interventions; 4) Bias due to deviations from intended interventions; 5) Bias due to missing data; 6) Bias in measurement of outcomes; 7) Bias in selection of the reported result. Within each domain, a series of 'signaling questions' elicit information relevant to risk of bias risk of bias assessment. The response options to the signaling questions are: “Yes”; “Probably yes”; “Probably no”; “No”; and “No information”.

A risk of bias judgement arising from each domain is generated by an algorithm, based on answers to the signaling questions. Judgement can be 'Low', ‘Moderate’, ‘Serious’, ‘Critical’. Overall risk of bias will be considered at 1) ‘Low risk of bias’ if all domains are at ‘low risk’; 2) ‘Moderate risk of bias’ if at least one domain is ‘moderate’ and no domain is ‘serious’ or ‘critical’; 3)’Serious risk of bias’ if at least one domain is ‘serious risk of bias’ and none at ‘critical risk of bias’; 4) ‘Critical risk of bias’ if at least one domain is at critical risk of bias.

The target trial will be conceptualized according to the approach used for randomized controlled trials in terms of population, experimental intervention, comparator and outcomes of interest.

The confounding domains considered will be the severity of COVID 19, comorbidities, age, and sex

Co-interventions that could differ between intervention groups and have an impact on study outcomes that we will consider are: antiviral treatment, antibiotic, corticosteroid.

2.6 Living systematic review approach

2.6.1. Steering committee

A steering committee of epidemiologists, methodologists, statisticians and clinicians with content expertise will be set-up. This committee will meet regularly, discuss the conduct of the project, difficulties encountered and possible changes in the protocol according to new knowledge available on this disease. Changes in the protocol could consist for example of changes in the search strategy, eligibility criteria (e.g., study design), research questions for the pairwise meta-analyses, outcomes.

2.6.2. Process and quality control

Our aim is to update the synthesis at least every week. For this purpose, we will search, screen and extract data every day. The updated synthesis will be reported at least every week.

To standardize the process and ensure both rapidity and quality, we will proceed as follow:

1) We will separate the process into different tasks and set up a team for each task (i.e., a researcher/volunteer will be involved in a single task). Each team will be led by a senior researcher ensuring the quality and standardization of the task.
2) For each task, we will develop a short training program for researchers/volunteers joining the team. This program will involve a) reading a manual detailing the task; b) performing the task on a sample as an exercise (e.g., evaluating the risk of bias of 3 studies), watching an online video providing the correction for the exercise and contacting the team leader to ask about difficulties; and c) after a successful training, the newcomer will perform the double data extraction with a senior well-trained researcher.
3) Each team will hold a weekly meeting to discuss difficulties and ensure standardization. All decisions and changes will be recorded.

4) We will develop an external quality control process for data collection involving senior researchers who will check a random sample of the data collected (e.g., member of the bias methods group for risk of bias)

We will consider the following tasks

1) Research mapping: screening and extracting data from registries
2) Screening databases from title/abstract to full text
3) Extracting data
4) Grading the evidence

The core team will perform the analysis, presentation and interpretation of the results.

2.6.3. Evolution of the protocol over time

The process will also evolve over time according to the new knowledge available regarding Covid-19.

The steering committee will systematically discuss and achieve consensus on the changes of protocol proposed.

2.7 Quantitative synthesis

2.7.1 Characteristics of eligible studies and evolution of evidence

At each update, we will first generate descriptive statistics for study and population characteristics to show the available comparisons, the amount of information and the distribution of important clinical and methodological variables (such as age, disease severity, comorbidities, location etc.). The data will be presented by pairwise comparison and network diagrams with nodes representing the interventions

being compared and lines representing the available direct comparisons in the studies. We will additionally use colours to represent the risk of bias of the studies in each direct comparison[15]. Using a contribution matrix,[16] we will show the effect of each piece of evidence in the full body of evidence and how new evidence affects the existing results.

2.7.2 Pairwise meta-analysis

For each direct comparison with at least two studies providing data, we will synthesize the results using as effect measures the risk ratio (RR) for dichotomous data, mean difference for continuous outcomes measured on the same scale and standardized mean difference (SMD) if the same outcome is measured in different scales, and hazard ratios for time-to-event data. We will present effect estimates with 95% confidence intervals (CIs). We use the random-effects model to incorporate the anticipated clinical and methodological heterogeneity across studies. We will use two assumptions for the between-study variance (τ^2): 1) a separate τ^2 for every comparison between two interventions and 2) a common τ^2 for studies comparing the same types of interventions. Visual inspection of forest plots, prediction intervals (the interval within which the effect of a future study is expected to lie[17]) and comparison of τ^2 with appropriate empirical distributions[18,19] will be used to assess the presence of important statistical heterogeneity.

2.7.3 Assessment of the transitivity assumption

Transitivity is the fundamental assumption of NMA and needs careful examination to reassure that results will be valid[20]. We will investigate the distribution of clinical and methodological characteristics that may act as effect modifiers across treatment comparisons. Such characteristics include age, severity status, comorbidity status, and country where care is delivered. To avoid intransitive networks, we will evaluate the similarity of studies comparing different sets of

interventions and only synthesize them when important clinical and methodological characteristics are sufficiently similar. We will also investigate whether different studies similarly define the interventions forming the nodes of the networks.

2.7.4 Network meta-analysis

For the sets of studies for which transitivity is likely plausible, we will perform random-effects NMAs to compare the different interventions or combination regimens and potentially obtain their ranking. We will assume a common heterogeneity parameter (τ^2) for every network of interventions. We will present the results in terms of effect sizes and 95% CIs in league tables and will use colours to represent the confidence in the evidence for every comparison. We will assess the impact of heterogeneity on the results by using prediction intervals. To rank the interventions, in the absence of excessive uncertainty in the relative effects, we will use the surface under the cumulative ranking curve (SUCRA)[21].

2.7.5 Assessment of incoherence

The conceptual evaluation of transitivity will be supplemented with a statistical evaluation of the assumption coherence, which refers to the agreement between direct and indirect evidence. We will use both local and global methods. Local approaches assess coherence in parts of the network but global approaches in the entire network jointly. Specifically, we will use the loop-specific approach[22], the side-splitting method[23] and the design-by-treatment interaction model[24]. Tests for incoherence are known to have low power, so we will interpret the results of the tests with caution.

2.7.6 Exploring heterogeneity and incoherence

If we find substantial heterogeneity or incoherence, we will use subgroup analyses and meta-regressions to explore the impact of the characteristics age, disease severity, comorbidity status, country where care is delivered, and time after the beginning of the outbreak. The characteristics explored will evolve and consider new knowledge on COVID-19. We will also explore case-mix heterogeneity using IPD, if available.

2.7.7 Bias due to missing results

We will assess the selective non-reporting or under-reporting of results in the studies identified according to the framework proposed in Chapter 13 of the Cochrane Handbook.[25]

We will use the comparison-adjusted funnel plot[15] (a modified funnel plot appropriate for NMA) and appropriate network meta-regression models[26] to assess the potential for small-study effects in each NMA. If asymmetry is found, we will explore possible reasons for the apparent association between study size and study effect. If publication bias is suspected, we will apply selection models that make assumptions about the probability of publication based on the study results[27].

2.7.8 Sensitivity analyses

We will perform sensitivity analyses by excluding studies at high risk of bias. We will also run the analyses using the number of participants analyzed instead of those randomized as well as by incorporating uncertainty in our missing outcome assumptions[28–30].

2.7.9 Implementation

We will run analyses and produce graphical displays using R (netmeta package[31]) and Stata (network[32] and network graphs packages[33]). Network meta-regressions will be run in a Bayesian environment using r2jags[34].

2.8 Evaluation of the confidence in the pairwise meta-analysis

To evaluate the confidence in the results of the pairwise comparisons for the primary outcomes, we will rely on the GRADE approach37. We will prepare 'Summary of findings' tables to present estimated relative and absolute risks. Two review authors will independently grade the overall certainty of the evidence for each outcome using the GRADE classification (GRADEpro GDT). We will include the primary outcomes listed in section 2.2 (outcomes) in the 'Summary of findings' tables.

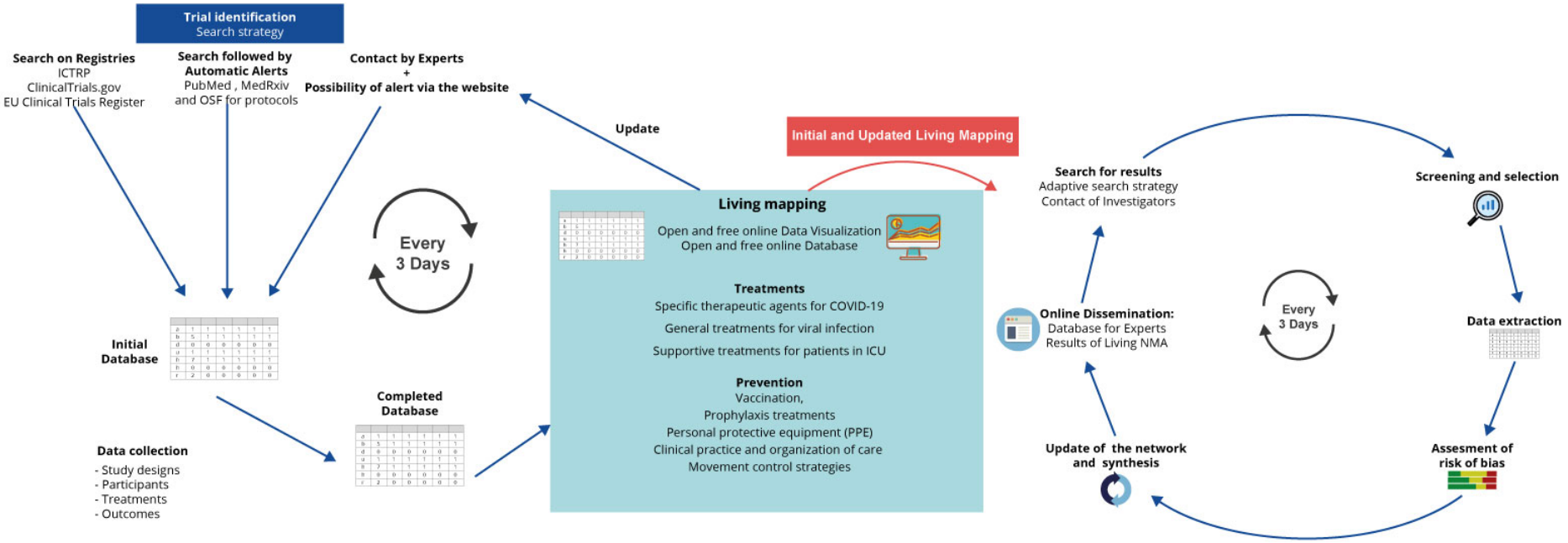
2.9 Evaluation of the confidence in the network evidence

To evaluate the confidence in the NMA results for the primary outcomes, we will use the CINeMA tool that considers the following domains: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence[35,36]. For within-study bias and indirectness, CINeMA calculates the contribution of each study in each network estimate and combines these contributions with the study-specific evaluations (low, moderate, high) to rate the relative effect for each comparison in the network. The domains of imprecision, heterogeneity and incoherence use a pre-specified clinically important size of effect to specify the margin of clinical equivalence between two interventions.

2.10 Data sharing

Study and participant characteristics, risk of bias data as well as outcome data will be made publicly available on a dedicated website as soon as they are extracted. We will develop a data-sharing plan to make the databases for registered and completed studies available once the data extraction process will be standardized in terms of the list of items to be extracted and the format of the databases.

Figure: Description of the process



3 REFERENCES

1. RKI - Coronavirus SARS-CoV-2 - SARS-CoV-2 Steckbrief zur Coronavirus-Krankheit-2019 (COVID-19) [Internet]. [cited 2020 Apr 6]. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Steckbrief.html#doc13776792bodyText3

2. Coronavirus Symptoms (COVID-19) - Worldometer [Internet]. [cited 2020 Apr 6]. Available from: https://www.worldometers.info/coronavirus/coronavirus-symptoms/

3. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi Zhonghua Liuxingbingxue Zazhi*. 2020 Feb 17;**41**(2):145–151.

4. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Internet]. 2020 Feb. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

5. Chinese Clinical Guidance For COVID-19 Pneumonia Diagnosis and Treatment [Internet]. *Am. Coll. Cardiol.* [cited 2020 Mar 20]. Available from: http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2020%2f03%2f17%2f11%2f22%2fchinese-clinical-guidance-for-covid-19-pneumonia-diagnosis-and-treatment

6. World Health Organization (WHO). A COORDINATED GLOBAL RESEARCH ROADMAP: 2019 NOVEL CORONAVIRUS. 2020 Mar;

7. Hernán MA, Robins JM. Causal inference: What if [Internet]. Available from: https://cdn1.sph.harvard.edu/wp-content/uploads/sites/1268/2020/02/ci_hernanrobins_21feb20.pdf

8. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019 28;**366**:l4898.

9. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016 Oct 12;**355**:i4919.

10. Coronavirus disease 2019 (COVID-19)Situation Report –56 [Internet]. 2020 Mar. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200316-sitrep-56-covid-19.pdf?sfvrsn=9fda7db2_2

11. Clinical management of severe acute respiratory infection when COVID-19 is suspected [Internet]. 2020 [cited 2020 Apr 6]. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

12. WHO Working Group on the Clinical Characterization of COVID-19 infection. A Candidate Core Outcome Measure Set for Clinical Research During the SARS-CoV-2/COVID-19 Pandemic. *submitted*.

13. Tallarita M, Iorio MD, Baio G. A comparative review of network meta-analysis models in longitudinal randomized controlled trial. *Stat Med*. 2019;**38**(16):3053–3072.

14. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007 Jun 7;**8**(1):16.

15. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoSOne*. 2013;**8**(10):e76654.

16. Papakonstantinou T, Nikolakopoulou A, Rucker G, et al. Estimating the contribution of studies in network meta-analysis: paths, flows and streams. *F1000Research*. 2018 pending for peer review;

17. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*. 2011;**342**:d549.

18. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012 Jun;**41**(3):818–827.

19. Rhodes KM, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *J Clin Epidemiol*. 2015 Jan;**68**(1):52–60.

20. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *ResSynthMeth*. 2012;**3**(2):80–97.

21. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *JClinEpidemiol*. 2011 Feb;**64**(1878-5921 (Electronic)):163–171.

22. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *JClinEpidemiol*. 1997 Jun;**50**(0895-4356 (Print)):683–691.

23. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *StatMed*. 2010 Mar 30;**29**(1097–0258 (Electronic)):932–944.

24. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and insconsistency in network meta-analysis: concepts and models for multi-arm studies. *ResSynthMeth*. 2012;**3**(2):98–110.

25. Higgins JPT, Chandler J, Cumpston M, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester (UK): John Wiley & Sons, Ltd; 2019.

26. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *ResSynthMeth*. 2012;**3**(2):161–176.

27. Mavridis D, Welton NJ, Sutton A, Salanti G. A selection model for accounting for publication bias in a full network meta-analysis. *Stat Med*. 2014 Dec 30;**33**(30):5399–5412.

28. White IR, Higgins JPT, Wood AM. Allowing for uncertainty due to missing data in meta-analysis--part 1: two-stage methods. *Stat Med*. 2008 Feb 28;**27**(5):711–727.

29. Mavridis D, White IR, Higgins JPT, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. *Stat Med*. 2015 Feb 28;**34**(5):721–741.

30. Chaimani A, Mavridis D, Higgins JPT, Salanti G, White IR. Allowing for informative missingness in aggregate data meta-analysis with continuous or binary outcomes: Extensions to metamiss. *Stata J*. 2018 Jul 1;**18**(3):716–740.

31. Rucker G, Schwarzer G. netmeta: An R package for network meta-analysis. *R Proj Website* [Internet]. 2013; Available from: http://www.r-project.org

32. White IR. Network meta-analysis. *Stata J*. 2015;**15**(4):951–985.

33. Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: The network graphs package. *Stata J*. 2015;**15**(4):905–950.

34. Su Y-S, Yajima M. R2jags: A Package for Running jags from R. 2009.

35. CINeMA: Confidence in Network Meta-Analysis [Software]. Institute of Social and Preventive Medicine, University of Bern [Internet]. 2017. Available from: cinema.ispm.unibe.ch

36. Nikolakopoulou A, Higgins JP, Papakonstantinou T, et al. Assessing Confidence in the Results of Network Meta-Analysis (Cinema). *bioRxiv*. Cold Spring Harbor Laboratory; 2019 Apr 5;597047.

37. Schünemann HJ, Higgins JP, Vist GE, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. *Cochrane Handb Syst Rev Interv*. John Wiley & Sons, Ltd; 2019. p. 375–402.

Appendix 1. CASE DEFINITIONS

(https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200316-sitrep-56-COVID-19.pdf?sfvrsn=9fda7db2_2)

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath), AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom onset.

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID19 case (see definition of contact) in the last 14 days before onset of symptoms;

OR

C. A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness breath) AND requiring hospitalization AND with no other etiology that fully explains the clinical presentation.

Probable case

A suspect case for whom testing for COVID-19 is inconclusive.

- Inconclusive being the result of the test reported by the laboratory

Confirmed case

A person with laboratory confirmation of COVID-19 infection, regardless of clinical signs and symptoms.

Appendix 2. Pharmacological treatment and non-pharmacological interventions of COVID-19. The list will be modified according to the evolution of the field. This list was established from the treatment evaluated in registered randomized controlled trials.

	Treatment type	Treatment name
Drugs	Antiviral, non-specific	Interferons Immunoglobulin Interleukin-2
	Antiviral, broad spectrum	Favipiravir Ribavirin Triazavirin Umifenovir Sofosbuvir+daclatasvir Sofosbuvir+ledipasvir Umifenovir+ribavirin Xiyanping
	Antiviral, antiretrovirals	ASC09 Azvudine Danoprevir Darunavir Darunavir+cobicistat Lopinavir+ritonavir Remdesivir Danoprevir+ritonavir ASC09+ritonavir
	Other antiviral	Baloxavir marboxil Oseltamivir
	Antiviral combination (when combining antivirals from different groups)	interferon alpha+lopinavir umifenovir+interferon alpha Lopinavir+ritonavir+ribavirin+interferon beta1 ASC09F+oseltamivir Ritonavir+oseltamivir lopinavir+ritonavir+xiyanping Lopinavir+ritonavir+interferon beta1
	Antimalaria	Chloroquine sulphate Hydroxychloroquine sulphate Dihydroartemisinin
	Antibiotics	Carrimycin
	Antiparasitics	Suramin sodium
	Non-specific anti-inflammatory	Methylprednisolone Other corticosteroids
	Immunosuppressant	Fingolimod

		Leflunomide Thalidomide
	Immunosuppressant+antiviral	Thalidomide+umifenovir
	Kinase inhibitors	Jakotinib hydrochloride Ruxolitinib
	Monoclonal antibodies	Adalimumab Bevacizumab Camrelizumab Eculizumab Mepolizumab PD-1 monoclonal antibody Sarilumab Tocilizumab Adamumab + tozumab Ixekizumab
	Antiviral+ monoclonal antibodies	Favipiravir+tocilizumab
	Antiviral+antimalaria	Darunavir+cobicistat+hydroxychloroquine Favipiravir+chloroquine phosphate
	Immunomodulator	CD24
	ACE inhibitor	Losartan
	Anticoagulant	Enoxaparin sodium
	Antiviral+antihistamine	Ebastine+interferon alpha
	Mucolytic	Acetylcysteine Bromhexine hydrochloride
	Other	Aviptadil (vasoactive intestinal peptide) Bismuth potassium citrate (may inhibit SARS-CoV1 helicase) Dipyridamole (antiplatelet) Pirfenidone (treat idiopathic pulmonary fibrosis) Polyinosinic-polycytidylic acid rhG-CSF Thymosin Tranilast Ulinastatin (sepsis management) Vitamin C Sodium Aescinate (vasoactive, organ protective) Tetrandrine (calcium channel blocker, anti-inflammatory) Lipoic acid injection (antioxidant) PUL-042 inhalation solution Noscapine (narcotine derivative) T89 (improving oxygen saturation)

Non-drug	Advanced Therapy Medicinal Products (ATMPs)	Aerosol inhalation of viral macrophage inflammatory protein Ankylosaurus; M1 macrophage target Convalescent plasma treatment Biological preparation of human placenta Umbilical cord mesenchymal stem cells Inactivated mycobacterium vaccine mRNA-1273 NK cells Recombinant cytokine gene-derived protein injection Washed microbiota transplantation
	Respiratory support	High-flow therapy with nasal cannulae Bag-valve mask oxygenation
	Organ support	Renal replacement therapy Artificial liver therapy Ozonated autohemotherapy
Prevention	Protective device	Medical mask N95 respirator
Post-COVID-19 management	Rehabilitation	Shadowboxing Pulmonary rehabilitation Lung rehabilitation training Ultra short-wave electrotherapy

Appendix 3. WHO Clinical Progression Scale, measured daily over the course of the study

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	**0**
Ambulatory	Asymptomatic; viral RNA detected	**1**
	Symptomatic; Independent	**2**
	Symptomatic; Assistance needed	**3**
Hospitalized: Mild disease	Hospitalized; no oxygen therapy	**4**
	Hospitalized; oxygen by mask or nasal prongs	**5**
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	**6**
	Intubation & Mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	**7**
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	**8**
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	**9**
Death	Dead	**10**

Notes.

1. If hospitalized for isolation only, record status as for ambulatory patient
2. If pO_2 not available, use SpO_2/FIO_2 ratio with a cutoff of 200 [18]

Appendix 4. Comment on the WHO progression scale

Below is reported the WHO progression scale used to define outcomes

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; Independent	2
	Symptomatic; Assistance needed	3
Hospitalized: Mild disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	6
	Intubation & Mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	7
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	8
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	9
Death	Dead	10

Another scale frequently use is reported below

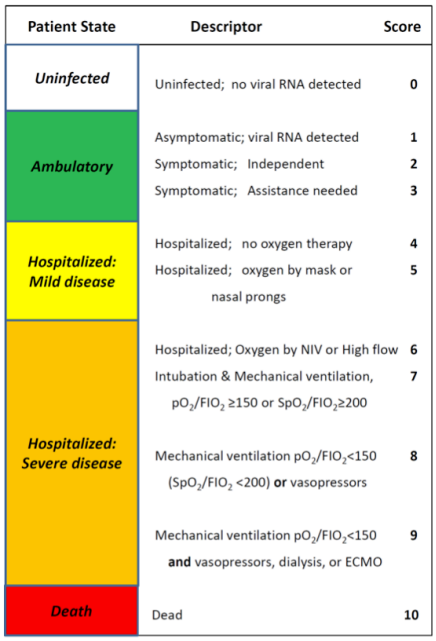
Ordinal Scale for Clinical Improvement

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

The 2 scales match as follow:

WHO progression scale (10 items)	Ordinal scale for clinical improvement
Level 5 or above	Level 4 or above
Level 6 or above	Level 5 or above
Level 7 or above	Level 6 or above

Below is reported the WHO progression scale used to define outcomes



Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; Independent	2
	Symptomatic; Assistance needed	3
Hospitalized: Mild disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	6
	Intubation & Mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	7
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	8
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	9
Death	Dead	10

Another scale frequently use is reported below

6 category scale
1—discharge (alive)
2—hospital admission, not requiring supplemental oxygen
3—hospital admission, requiring supplemental oxygen
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation
6—death

The 2 scales match as follow:

WHO progression scale (10 items)	**6 category scale**
Level 5 or above	Level 3 or above
Level 6 or above	Level 4 or above
Level 7 or above	Level 5 or above