# Modifications to the Master protocol “Interventions for the prevention and treatment of COVID‐19: a living mapping of research and living network meta‐analysis”

Below is the list of changes done from the main master protocol published on Cochrane Library (10.1002/14651858.CD013769) on the 3rd of November 2020.

We report hereby the changes by review.

## Pharmacological treatments review:

Below are the changes made in the review compared to the protocol:

### Screening and eligibility criteria:

As of March 1, 2022, the COVID-NMA revised its protocol to include only studies evaluating immunomodulators and antiviral therapies. Comparisons evaluating antivirals and immunomodulators will continue to be updated every two weeks.

For treatments that are neither immunomodulators nor antivirals, we present online the updated results up to Feb 28, 2022 including all identified reports through our search strategy up to this date.

As of December 2021, we continue to conduct screening on a weekly basis rather than on daily basis.

Given the increase in the number of randomized controlled trials, we decided to stop extracting data from Non-Randomized Studies as of Sep 2, 2020.

### Outcomes:

January 27, 2021:

To avoid multiplicity, we reduced the number of outcomes evaluated in the review. We considered only two time-points (D28 and ≥ D60) for the following outcomes:

clinical improvement, WHO score 7 or above, and all-cause mortality.

We considered the outcome Viral negative conversion (D7) outcome as critical outcome.

We removed the outcome “WHO Clinical Progression Score level 6 or above” and “time to WHO Clinical Progression Score 6 or above” since the definition used in the studies appears to be subject to variation due to local guidelines and resources. It is therefore an unreliable or inconsistent indicator when assessed across studies.

March 2021:

Hospitalization or death outcome was added as a new outcome for the outpatient setting review.

### Data extraction:

As of March 2021, we made modification on the data extraction form to consider specific variables for studies conducted in outpatients’ settings and included one additional outcome on hospitalization or death. Studies conducted in ambulatory outpatient setting are not to be pooled with hospitalized setting. A separate analysis and grade for outpatients setting was performed as of April 2021.

### Risk of bias assessment:

October 2020: For Rob domain 2, we stopped to consider anticoagulants as a relevant co-intervention for assessing risk of bias in the domain deviations from intervention. The decision was made after discussion with content experts. It is only of concern for anticoagulant studies.

April 2021: We decided not to consider any cointervention relevant for studies conducted for outpatient setting.

### Contact authors:

As of April 2021, following changes in the eligibility criteria, we continued to contact authors of studies included in the meta-analyses of antivirals and immunomodulators only.

Later in August 2022, we continued to contact authors of studies to be included in the NMA-immunomodulators only.

### Analysis:

We modified our protocol to consider providing updated analysis and grade evaluation every two weeks instead of every week.

Specific analysis for outpatient setting review as of April 2021.

### Subgroup analyses:

We decided to conduct post-hoc subgroup analysis to explore the impact of the funding source (public or non-profit/mixed or private) and conflict of interests.

The subgroup analyses planned to explore age, sex and

comorbidity status and time after the beginning of the outbreak are not conducted.

### Grade:

For assessing imprecision in GRADE, as of July 2022, we stopped to consider the relative risk and standard MIDs of 0.75 and 1.25 as thresholds of an effect. Instead, we use the minimally contextualized approach. We modified the approach to consider the size of the absolute risk and its confidence intervals and have set minimal important difference thresholds at 5% (50 per 1000) for the outcomes of clinical improvement, time to clinical improvement, and adverse events. For the outcomes of mortality, time to death, WHO score 7 and above, time to WHO score 7 and above, and serious adverse events we have set the threshold at 1% (1 per 1000). Absolute differences smaller than 5% (or 1% respectively) are considered to indicate trivial/no effect and differences of more than 5% (or 1% respectively) are considered a clinically important benefit/harm.

## Preventive trials review:

Specific outcomes were added to this review similar to the vaccine review.

List of critical outcomes:

* Incidence of symptomatic COVID-19 (confirmed with positive test for SARS-CoV-2 infection by RT-PCR or probable
* Incidence of COVID-19 confirmed with positive test for SARS-CoV-2 infection by RT-PCR
* Hospital admissions or death
* All-cause mortality

In addition to the following safety outcomes for prevention of COVID-19:

* Incidence of serious adverse events (SAEs)
* Incidence of any adverse events List of critical outcomes:
* ICU admissions or death
* Incidence of symptomatic COVID-19 (confirmed with positive test for SARS-CoV-2 infection by RT-PCR or probable or suspected) or asymptomatic COVID-19 confirmed with positive test for SARS-CoV-2 infection by RT-PCR

The COVID-NMA stopped including preventive treatment trials. The analysis presented online includes preventive trials identified and included up to Oct 22, 2021.

## Non-pharmacological interventions review:

As of March 1, 2022, we stopped including NPT trials. The analysis presented online includes preventive trials identified and included up to March 1, 2022. (some comparisons in it have oct 22, as last search date)

## Vaccine trials review

Modifications made to the protocol are posted on zenodo: <https://doi.org/10.5281/zenodo.7198128>

Below we list major changes to the protocol published on zenodo  at [doi.org/10.5281/zenodo.6458272](https://zenodo.org/record/6458272) and registered on PROSPERO ([www.crd.york.ac.uk/prospero/display\_record.php?ID=CRD42021271897](https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021271897)).

### Outcomes:

* Incidence of confirmed symptomatic Covid-19 after first dose confirmed with positive test for SARS-CoV-2 infection by RT-PCR or NAAT or any other validated test.
* Incidence of participants with confirmed SARS-CoV-2 infection after first dose confirmed by RT-PCR or Nucleic acid amplification testing (NAAT) or any other validated test (symptomatic or asymptomatic).
* Incidence of withdrawals due to adverse events.
* We also clarified some outcomes: For the outcome “specific adverse events” we collected data for “nervous system diseases” (instead of stroke, headache, delirium, and paraesthesia) since we found this was reported more often. We didn’t collect data on “bruising.”
* We changed the description of the outcome systematic adverse events and local adverse events to Systematic reactogenicity events and local reactogenicity events to define immediate, short in term and usually expected adverse effects.

### Contact authors:

Due to limited resources, we will not contact study authors yet for missing results.

### Analysis:

As of December 2021, we modified our protocol to consider providing updated analysis every two weeks.

## Vaccine observational review:

In April 2021, we decided to include vaccine observational studies and to provide living evidence synthesis for vaccines effectiveness against variants of concern. The project was stopped on Nov 3 2022 as last screening date and end of Nov 2021 for completion of committed objectives.