INPLASY PROTOCOL

To cite: Gupta et al. Medical And General Interventions for treatment of Coronavirus disease 2019 (MAGIC): protocol for systematic review and meta-analyses of randomized controlled trials. Inplasy protocol 202090092. doi: 10.37766/inplasy2020.9.0092

Received: 26 September 2020

Published: 26 September 2020

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Support: **None.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Medical And General Interventions for treatment of Coronavirus disease 2019 (MAGIC): protocol for systematic review and meta-analyses of randomized controlled trials

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Review question / Objective: **Does any investigational medical therapy such as Hydroxychloroquine, Remdesivir, Steroids, Convalescent Plasma, or Tocilizumab improve outcomes in COVID-19 compared to the current standard of care/placebo treatment.**
Condition being studied: **COVID-19.**
Information sources: **For this review, it is crucial to identify relevant results as rapidly as possible. Priority sources for retrieval of studies include the WHO International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/ictrp/en/); PubMed (https://pubmed.ncbi.nlm.nih.gov) and its curated version LitCOVID; and MedRxiv (https://www.medrxiv.org). Literature search strategy (Appendix B) without any language restrictions with cut-off date of 25th September 2020 has been devised in accordance with international guidelines which can be updated and modified based on availability of new eligible resources and Cochrane living registry of COVID-19 studies. Reference list of selected articles will also be screened for identifying additional potentially eligible studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 September 2020 and was last updated on 26 September 2020 (registration number INPLASY202090092).

INTRODUCTION

Review question / Objective: **Does any investigational medical therapy such as Hydroxychloroquine, Remdesivir, Steroids, Convalescent Plasma, or Tocilizumab improve outcomes in COVID-19 compared to the current standard of care/placebo treatment.**

Rationale: **Currently there are no approved drugs for the treatment of COVID-19.**

Multiple randomized controlled trials (RCTs) are evaluating medical and/or general pharmacological interventions to improve outcomes in this disease. However most trials are small and underpowered to detect clinically significant and/or statistically significant differences. Hence the need to pool data from smaller RCTs to arrive at the best available evidence to guide decision-making.

Condition being studied: COVID-19.

METHODS

Participant or population: All patients with COVID-19.

Intervention: Medical and/or general pharmacological treatment specifically Hydroxychlorquine, Remdesivir, Steroids, Convalescent Plasma, or Tocilizumab.

Comparator: Standard of care/placebo.

Study designs to be included: Only randomized controlled trials (RCTs).

Eligibility criteria: Randomized controlled trials with relevant extractable data.

Information sources: For this review, it is crucial to identify relevant results as rapidly as possible. Priority sources for retrieval of studies include the WHO International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/ictrp/en/); PubMed (https://pubmed.ncbi.nlm.nih.gov) and its curated version LitCOVID; and MedRxiv (https://www.medrxiv.org). Literature search strategy (Appendix B) without any language restrictions with cut-off date of 25th September 2020 has been devised in accordance with international guidelines which can be updated and modified based on availability of new eligible resources and Cochrane living registry of COVID-19 studies. Reference list of selected articles will also be screened for identifying additional potentially eligible studies.

Main outcome(s): The current selection of outcome measures is primarily based on the outcome sets developed by the WHO for research in COVID-19 hospitalized patients identified through the COMET initiative (http://www.comet-initiative.org/Studies/Details/1538), which is expected to evolve over time. However, the main outcomes would still pertain to demonstrable clinical benefit and death from any cause in this systematic review and meta-analyses. (A) For mild/moderate case subgroup, primary outcome of interest would be clinical improvement: • Clinical benefit measured on WHO ordinal scale [16] for clinical improvement (Appendix A) or its modifications or any other similar ordinal scale. Relevant endpoints would include time-to-clinical improvement (TTCI) and proportion of patients improved by Day 7, Day 14, Day 28 of diagnosis (B) For moderate to severe/critical case subgroup, primary outcome of interest would be mortality: • All-cause mortality. Relevant endpoints would include early (Day 14) mortality or late (Day 28-30) mortality as reported in individual trials Secondary outcomes for both the subgroups would include • Time to 2019-nCoV reverse transcriptase polymerase chain reaction (RT-PCR) negativity • Viral negativity on specified days (D3, D7, D14) as reported in individual trials Safety outcomes for both subgroups would include • Serious adverse events (Grade 3 or worse toxicity).

Data management: 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. A review-specific structured data extraction form will be used to ensure consistency of information. Data extracted will include study characteristics (such as first author, publication year and journal), number of participants randomised, patient characteristics (severity of clinical presentation), intervention details (class and type of treatment), outcome measures, and risk of bias assessment. For dichotomous outcomes, the number of events and number of total participants in each study arm will be extracted. For continuous outcomes, standard deviations (SDs) and number of total participants per

study arm will be extracted. When SDs are not available but standard errors, t-statistics or p-values are reported, they will be extracted and transformed to SDs when possible. For missing outcome data, number of participants who dropped out before the completion of the study and how missing outcome data were handled by the study authors will also be reported. Authors may be contacted for updates or retrieval of any missing information considered relevant for the purpose of the systematic review.

Quality assessment / Risk of bias analysis: This systematic review will be carried out in accordance with Cochrane methodology for systematic reviews of interventional studies [11]. The analysis, interpretation, and reporting of results will include a risk of bias assessment using the Cochrane of Bias tool [12] for all included individual studies. Included studies will be considered to have low, unclear, or high risk of bias according to assessment on the following items: random sequence generation and concealment of allocation (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessors (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and any other sources of bias that could influence the quality of the study. Quality of evidence and strength of recommendation will be based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach [13] that defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. It involves consideration of within-study risk of bias (methodological quality); directness of evidence; heterogeneity; precision of effect estimates; and publication bias for each individual outcome. All analyses will be done using Review Manager.

Strategy of data synthesis: Evidence synthesis: For each direct comparison meta-analysis for each of the five interventions of interest (hydroxychloroquine, remdesivir, steroids, convalescent plasma, tocilizumab), data from at least two studies will be pooled in a random-effects model to compute summary point estimates with 95% confidence intervals (CIs). Relative risk (RR) will be used as outcome measures for dichotomous data, while mean difference or standardized mean difference (SMD) will be used for continuous outcomes. Sensitivity analysis will be performed and potential publication bias will be assessed in each of the individual direct comparison meta-analysis through appropriate statistical testing. Trial sequential analyses: Due to continuous inclusion of new trials necessitating repetitive testing of accumulating data for updating the evidence, this systematic review will also attempt to perform trial sequential analyses for all outcomes in order to calculate the required information size (number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of the relevant trial sequential monitoring boundaries as outlined in the trial sequential analysis manual (https://www.ctu.dk/tsa/files/tsa_manualpdf).

Subgroup analysis: Appropriate subgroup analysis will be done based on disease severity.

Sensibility analysis: Sensitivity analysis will be done by dropping individual trial and assessing its impact upon the point estimates and 95% confidence intervals.

Language: English.

Country(ies) involved: India.

Keywords: COVID-19; medical therapy; randomized; meta-analysis.
Dissemination plans: Publication in peer-reviewed journals.

Contributions of each author:
Author 1 - Tejpal Gupta - Design and protocol writing, statistical analysis & interpretation, and drafting of manuscript.
Author 2 - Babusha Kalra - Literature search, data extraction, and manuscript editing.

Author 3 - Prafulla Thakkar - Literature search, data extraction, and manuscript editing.
Author 4 - Sadhana Kannan - Statistical methods (analysis, interpretation, & reporting) and manuscript review.