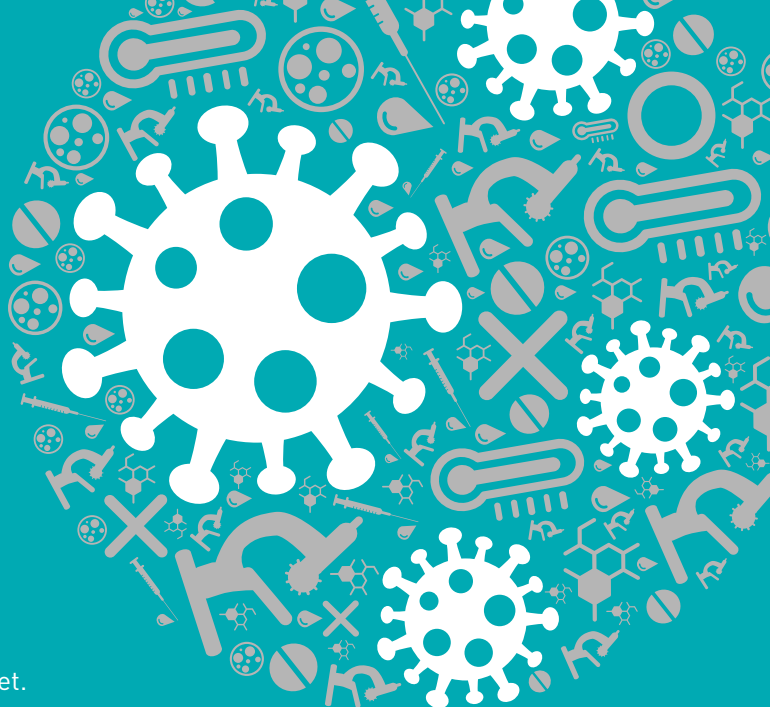


COVID-19 RESEARCH STUDIES FACT SHEET

ACADEMY OF SCIENCES MALAYSIA (ASM)

ASM is a statutory body of eminent Malaysian scientists elected for their contributions to science. At this period of unprecedented uncertainty due to the Covid-19 pandemic, ASM has established a Special Interest Group (SIG) on COVID-19 comprising Fellows of the Academy, Young Scientists Network (YSN-ASM) and Top Research Scientists Malaysia (TRSM) who are the expert network of ASM to review key research findings around the world and issue fact sheets to help the public understand the implications (and limitations) of the research studies. This factsheet briefly describes the clinical trials for potential COVID-19 medications. A few terminologies on clinical trials and drug use are also introduced in this factsheet.



CLINICAL TRIALS FOR COVID-19

Therapeutic options for COVID-19 patients

There are **no proven treatments** for COVID-19. Current clinical management is directed at relieving symptoms and supportive care, i.e. maintaining fluid status and nutrition, and supporting physiological functions.

Efforts are levitated to develop COVID-19 therapeutics. Currently, COVID-19 patients are receiving either chloroquine, hydroxychloroquine, lopinavir-ritonavir, favipiravir, remdesivir, azithromycin, ribavirin, interferon, convalescent plasma, steroids, or anti-IL-6 as treatment agents. The therapeutics are based on their *in vitro* antiviral and/or anti-inflammatory properties. **The prescribing should be done on a case-by-case basis** by trained clinicians to avoid undesirable side effects and contraindications.

Therapeutic Rationale for Drug Repurposing in COVID-19

All the drugs mentioned above are repurposed, off-label, and are of compassionate use natures.

How can repurposing drugs help? The conventional anti-SARS-CoV-2 drug discovery from scratch is time-consuming. A licensed drug or one that is already under investigation and development would have passed phase 1 trials and is expected to reach patients more quickly.

However, there is one obvious disadvantage of this drug repurposing route: there is **no efficacy and safety evidence** of the drugs (in fact, **any drugs**) targeting SARS-CoV-2 in humans. Therefore, there is a global effort to accelerate clinical trials of various therapeutic agents to evaluate their safety and efficacy in COVID-19 patients.



What is drug repurposing? Drug repurposing, also known as drug reprofiling or drug repositioning, is the process of “redeploying a drug that is already approved to treat one disease to see if it works for a different disease”.

What is off-label use? Off-label use (of a drug) is the use of a licensed drug for indications that have not been approved by a regulatory authority. For example, the antimalarial drug, chloroquine or the related hydroxychloroquine is used for inflammatory disorders, but it is now used to treat COVID-19.

What is compassionate use? It is the use of a new drug to treat a certain disease when no other treatment options are available. Remdesivir is an example of a compassionate use drug for COVID-19 as it is yet to be approved by any legal authority.

Clinical trial for COVID-19

Several promising agents for COVID-19 treatment that are currently in clinical trial pipelines, to name a few:

- **Remdesivir** (still an investigational agent)
- **Lopinavir/ Ritonavir** (approved for HIV use) with or without interferon
- **Hydroxychloroquine and chloroquine** (oral prescription drugs for treatment of malaria and certain inflammatory conditions)
- Other drugs (investigational antivirals, immunotherapeutic, and host-directed therapies)
- **Favipiravir** (antiviral for influenza use)
- **Tocilizumab** (immunosuppressive monoclonal antibody for rheumatoid arthritis, IL-6 inhibitor)
- **Convalescent plasma therapy** (adaptive immunotherapy used in the treatment of SARS, MERS, and 2009 H1N1 pandemic)

A number of trials of different scales are underway to study different treatments, some of which are funded by different pharmaceutical companies and initiated by different medical institutions (Table 1). Universiti Malaya Medical Centre is initiating a clinical trial using tocilizumab starting middle of April 2020.

Malaysia is also one of the countries in the global Solidarity trial launched by the World Health Organization (WHO) mainly looking at the safety and effectiveness of remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with Interferon beta-1a, and chloroquine or hydroxychloroquine. The rationale of this global Solidarity trial is to recruit as many patients as possible over 90 countries by providing them with standardized trial design. Through this initiative, faster results will be generated, hence providing collectively strong evidence to determine the relative effectiveness of potential treatments.

Table 1: A few clinical trials of SARS-CoV-2 infection and treatment of patients with mild, moderate, and severe COVID-19

Therapy	Study	Participating countries	Phase
Remdesivir	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults	US, Denmark, Germany, Japan, Korea, Mexico, Singapore, UK	3
Lopinavir/ Ritonavir	COVID-19 Ring-based Prevention Trial With Lopinavir/Ritonavir	Canada	3
Lopinavir/ Ritonavir, Hydroxychloroquine	Randomized Controlled Clinical Trials of Lopinavir/Ritonavir or Hydroxychloroquine in Patients with Mild Coronavirus Disease (COVID-19)	Korea	2
Tocilizumab	Multicenter Study on the Efficacy and Tolerability of Tocilizumab in the Treatment of Patients With COVID-19 Pneumonia	Italy	2
Convalescent plasma	Convalescent Plasma to Stem Coronavirus: A Randomized, Blinded Phase 2 Study Comparing the Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19	US	2

Source: clinicaltrials.gov



What is an adaptive study? A study that allows modifications to the study design based on accumulating data obtained from the trial.

What is a multicentre study? A study that is carried out at more than one medical institution.

What is a randomized study? A study design that randomly assigns participants into an experimental group or a control group.

What is a controlled study? A study whereby one of the interventions is the standard of comparison or control.

What is an open-label study? A study whereby both the researchers and participants know which drug (or intervention) is being given to participants.

What is a blinded study? A study whereby the participants do not know (is blinded as to) what treatment they are receiving.

What is a Phase 2 study? A stage in clinical trials that collect preliminary data on whether a drug works for a certain condition/disease (testing the drug's effectiveness).

What is a Phase 3 study? A stage in clinical trials to collect information about a drug's safety and effectiveness by studying different dosages or drug combination. This phase typically involves more participants.

Ethics of Clinical Trial for COVID-19

Preserving clinical trial integrity while ensuring participant health and safety during the coronavirus pandemic is very important. One concern is whether it is ethical to give patients a placebo (a substance that has no therapeutic effect) during this pandemic. It is argued that a placebo group (receiving the established standard of care) would be safer than the experimental group (receiving new drugs). As compared to randomised trials, single group cohorts or studies without controls may be less safe and might lead to the delay in discovering a new therapy. Optimally, an adaptive design approach should be prioritised to allow modification of certain experimental design. Ethics approval and trial protocol also need to be promptly initiated and approved without overlooking the scientific validity, and participants' rights and safety in studies conducted during any infectious disease outbreaks.



TAKE HOME MESSAGE

With the current COVID-19 pandemic, more clinical trials are needed to discover and validate new therapies, otherwise, there will be no proven treatments for future coronavirus pandemics.

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References

- FDA. Coronavirus Treatment Acceleration Program (CTAP). www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap
- FDA. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards. www.fda.gov/media/136238/download
- FDA. “Solidarity” clinical trial for COVID-19 treatments. www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
- Kalil AC. Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. JAMA. Published online March 24, 2020. doi:10.1001/jama.2020.4742
- McDermott MM, Newman AB. Preserving Clinical Trial Integrity During the Coronavirus Pandemic. JAMA. Published online March 25, 2020. doi:10.1001/jama.2020.4689

