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IMPACT OF COVID-19 ON CLINICAL TRIALS

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Impact of COVID-19 on Clinical Trials

Abstract

As the COVID-19 pandemic continues to ravage countries, all attention is focused on the research community to generate evidence-based preventive treatment, primarily through Clinical Trials (CTs). With close to 2,500 CT studies being conducted worldwide, it is of paramount importance to understand the nature of CTs being conducted globally and in India, the underlying factors that oversaw the CT boom and the role of regulatory bodies. The paper also attempts to evaluate the ramifications of COVID-19 on CTs globally through the lens of regulatory policies like Emergency Use Authorisation in the United States, the ethical conundrums surrounding scientific publishing and the trickle-down effect of these on developing nations like India. In India, in addition to CTs, ICMR—based on observational studies—has recommended the use of HCQ as a prophylactic for healthcare workers. While these observational studies may be an indicator of the drug's efficacy as a preventive, it is always apt if backed by scientific evidence, given the widespread administration of HCQ amongst healthcare workers. Under such circumstances, while timely vaccine development is certainly critical, it is equally important to safeguard the CT research standards and procedures.

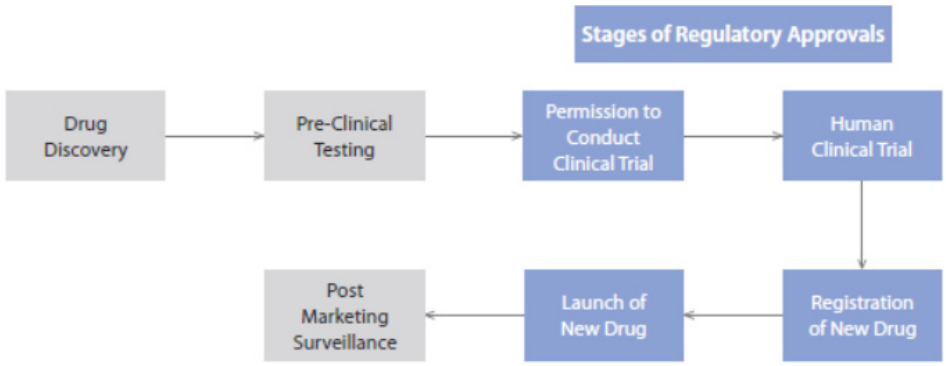
Introduction

A systematic study of a new drug in humans in order to generate data to verify clinical, pharmacological and adverse events if any, and consequently establish evidence regarding safety and efficacy of the drug is referred to as Clinical trials (CTs)].[1] CTs are an indispensable part of the drug development process, given 90 per cent of CTs fail despite the drug showing high efficacy under laboratory conditions. While stringent regulatory norms, which ensure only products of high safety and efficacy reach the patients, are often cited as the reason, reports show that 50 per cent of the drugs have failed due to lack of efficacy.[2] Most of them fail to adhere to the research protocols or generate data inconsistencies resulting in rejection by the regulatory agency. This proves to be costly for the drug manufacturers as CTs, which are the pre-approval stage, constitute 70 per cent of the drug development costs[3] Advancements in R&D have ensured that while objectives of drug discovery remain the same, the methodologies allow Pharma companies to identify target molecules at a faster rate. Increased pressure on accelerating drug development and reducing costs has left Pharma companies scrambling to look for newer ways to outsource patients.

Historically until the post WTO period, CTs were conducted in Western countries, predominantly the United States. In the initial years, CTs were done by Pharma companies in lieu with research institutions with researchers acting as the Principal Investigator (PI). Since then, the discovery of a larger number of drug molecules mediated the rise of specialised CT centres called Contract Research Organisations (CROs) which tried to stem the gap between the Pharma companies and patient pool by providing services like clinical operations, quality assurance and data management leaving Pharma companies to focus on drug discovery and sales. The biggest

1. CDSCO–New Drugs and Clinical Trial Rules, 2019. https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdfdocuments/NewDrugs_CTRules_2019.pdf.
2. Plaford, Chris. 2015. "Why Do Most Clinical Trials Fail?" *Clinical Leader*, July 8, 2015. https://www.clinicalleader.com/doc/why-do-most-clinical-trials-fail-0001.
3. Maiti, R., and Raghavendra M. 2007. "Clinical Trials in India." *Pharmacological Research* 56(1):1–10. doi: 10.1016/j.phrs.2007.02.004.

Figure 1: Stages of Regulatory Approval in the Process of Drug Development[4]



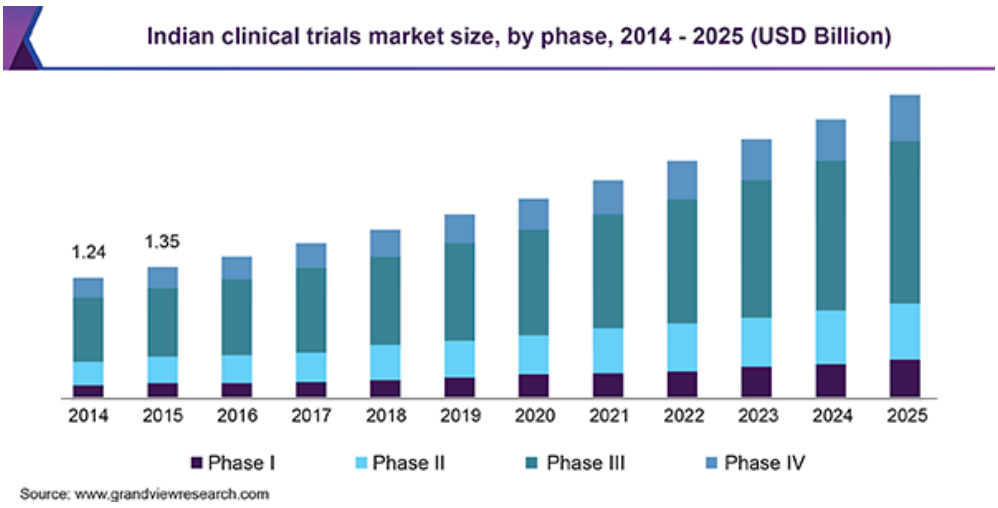
challenge for CROs was to recruit enough patients for CTs as increasingly stringent regulations and detailed compensation increased research costs further. A lack of interest from patients due to increasing awareness and fall in the number of investigators led to Pharmaceutical companies expanding towards newer markets like India and China.[3]

Indian Context

Indian CTs market is expected to reach US$ 3.1 bn by 2025, registering a CAGR of 8.7 per cent during this time period. Globalisation of CTS, newer emerging technology and slightly relaxed regulations are expected to be the growth drivers of this market.[5]

In the years preceding 1990, India was not a favoured destination for CTs for global drug makers, but that changed with the advent of new Asian economies. India is home to 17 per cent of the world population; around 20 per cent of the global diseases are born here, offering an attractive patient pool for drug companies.[4] Factors like cheap labour and infrastructure, English-speaking investigators and speedy regulatory approval could translate into approximately 60 per cent cost reduction for drug makers.[6] It would also help companies establish a presence in the countries given the burgeoning healthcare requirements. Even though India had adopted the ICH-GCP guidelines, it was only in 2005 India became a signatory to the TRIPS Agreement which provided patent protection in line with the

Figure 2: Estimated Indian Clinical Trials Market



4. Mehdi, Ali, Rahul Mongia, Deepmala Pokhriyal, and Seema Rao. 2017. *Challenges and Prospects for Clinical Trials in India: A Regulatory Perspective*. New Delhi: Academic Foundation.
5. Indian Clinical Trials Market Analysis Report By Indication (Oncology, Autoimmune), By Phase (I/II/III/IV), By Study Design (Interventional, Observational), Vendor Landscape, And Segment Forecasts, 2018 – 2025. December 2018. Research and Markets.
6. Bhowmik, D., M. Chandira, and B. Chiranjib. 2010. "Emerging Trends of Scope and Opportunities for Clinical Trials in India." *International Journal of Pharmacy and Pharmaceutical Sciences* 2(1):7–20.

WHO guidelines that saw a boom in the number of CTs held countrywide. From 2005 to 2013, the global share of CTs grew with faster recruitment process, better Return on Investment (RoI) and competitive advantage translated into revenue implications.[7] On her part, India stood to gain access to technological innovation and investment benefits seeking to build its healthcare facilities.

After the TRIPS Agreement, the number of CTs being conducted surged, but lack of stringent laws led to inadequate compensation and even death of the participants. The late 2000s saw several reports and complaints about abuse of patients, data fraud and ethical concerns regarding patient consent. Following protests from various NGOs and the Human Rights Commission, the CT regulations came under the scanner. In an affidavit, the Centre admitted that close to 2644 people had died during 475 CTs for new drugs during 2005–2012. Around 11,972 serious adverse events (excluding death) were reported from January 1, 2005 to June 30, 2012, out of which 506 were attributed to CTs.[8] This prompted the Supreme Court to issue a directive stopping all CTs in the country until amendment of the regulatory framework incorporating concerns on ethics, data management and other challenges was implemented. The Health Ministry instructed the sponsors of the trials to pay the participants 60 per cent of the compensation upfront in case of death or permanent damage which caused firms to shift trials out of the country. In 2013, of 1,80,649 CTs in 178 countries, only 1.4 per cent or 2,563 studies were conducted in India.

The growing decline in the number of CTs in India prompted healthcare researchers and WHO officials to emphasise that India will miss out on global attention for clinical research due to its stringent clinical laws. The criticality of this is demonstrated by the rising unmet healthcare needs, changing profile of the nature of diseases and lack of healthcare innovation.

In 2019, the New Drugs and Clinical Trials (NDCT) Rules, 2019 was enacted by the Ministry of Health and Family Welfare which replaced/modified certain sections of the existing Drugs and Cosmetics Rules, 1940 focusing on promoting CTs in the country.

Conducting Trials in India

1) Opportunities

a) High Patient Enrolment Rate

When compared to the United States which has an enrolment rate of 0.3 patients per month, India has an enrolment rate of 3 patients per month. Given the financial constraints and the high incidence of communicable and non-communicable diseases, the marginalised section can rarely afford treatment. This pushes them towards CTs. McKinsey estimates that India has one of the highest patient enrolment rates compared to other countries.[9]

b) Human Resources and Technical Expertise

CT requires trained investigators since it is highly labour intensive. Industry reports suggest that India has about 500 investigators, over 57,200 doctors, 43,222 hospitals and dispensaries and 8.7 lakh beds including both private and public hospitals.[10]

c) Diverse Patient Pool

Given the heterogeneity and diverse pool of population even within the country and treatment-naïve patients with high incidence of diseases universal to both developed and developing countries, patient recruitment is easier than in the United States.

d) Cost Advantage

The unit cost of conducting trials in India is much lower than other countries. India comes 4th amongst all nations after Russia, Argentina

7. Mondal S., and Abrol D. 2015. "Clinical Trials Industry in India: A Systematic Review." *Sama*, March 15, 2015.
8. Dutta, Nirmalya. 2013. "No more Clinical Trials till You can Monitor Them: Supreme Court to Centre." *The Health Site*, October 1, 2013. www.thehealthsite.com/news/no-more-clinical-trials-till-you-can-monitor-them-supreme-court-to-centre-84170/.
9. Kent, Chloe. 2019. "Indian Health Ministry Fast-tracks Drug Approvals with New Clinical Trial Legislation." *Clinical Trials Arena*, March 26, 2019. https://www.clinicaltrialsarena.com/news/indian-clinical-trial-regulation-new-rules/.
10. Ravindran P. 2004. "Clinical Trial on Trial." *The Hindu Business Line*, November 1, 2004. https://www. thehHindubusinessline.com.

and China under clinical cost minimisation. Studies show that compared to the 1-unit cost of CT in the United States, it can be reduced to as much as 0.11 unit cost in India.[7]

Other factors that go into market selection for CTs are presence of CROs in the country, health infrastructure and number of CTs conducted historically which showcase the level of experienced investigators available.

2) Challenges

a) Red Tape Hurdle

The regulatory approvals are still delayed in India compared to counterparts in Canada, where approval takes as less as 30 days. Attributed to low funding and inadequate staff at the regulatory agency, a hassle-free process is absent.

b) Ethical Hurdles

The concept of informed consent is lacking and patients are exploited due to lack of education and awareness.

c) Presence of Non-Accredited CROs

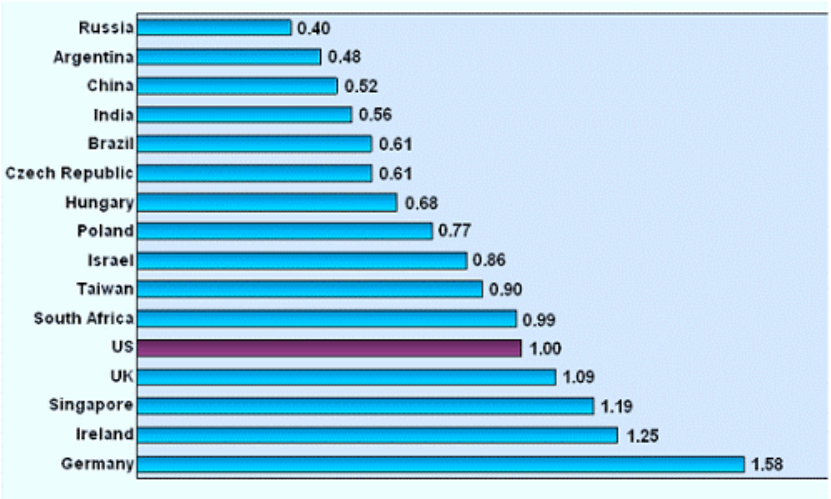
Regulatory Bodies and Frameworks

The Central Drugs Standard Control Organisation (CDSCO), governed by the Ministry of Health and Family Welfare, is the national regulatory authority of India which lays down standards and guidelines for the approval of drugs, cosmetics, diagnostics and devices. It aims to coordinate the activities of the State Drug Control Organisations and provide expert advice with the intent of standardising the enforcement of the legislation. They are also critical in regulating clinical research and introducing new drugs for public use across the country. The Drug Controller General of India (DCGI) is the regulatory body responsible for issuing permissions for the conduct of CTs as well as marketing licenses for drugs in India. The DCGI is supported by various agencies like the Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT) in the conduct of biomedical research and evaluation of CTs.

Before 2019, CTs in India were under the Drug and Cosmetic Rules 1945 (D&C Rules) as detailed in Schedule Y. In 2013, modifications regarding compensation of trial participants in the event of death or injury during a CT were incorporated under Rule-122DAB inserted into the D&C Rules, 1945. The compensation amount was to be decided by a Licensing Authority. Rule 122-DAC inserted into the D&C Rules, 1945 detailed on the conditions under which CTs are to be conducted, including approval from an Ethics Committee, registration with the Clinical Trial Registry-India (CTRI) and reporting adverse events immediately.

The NDCT Rules came into force on March 19, 2019 intending to promote CTs in India. The new regulations

Figure 3: Cost (manpower, rental, IT and operational costs) of conducting CTs in India vs other countries



- The cost of conducting CR in Russia, Argentina, China & India is about half the cost to the US (manpower, rental, IT & operational costs)

will allow drugs licensed for use in the United States and Europe to be approved automatically in India without due process, provided the CT includes Indian patients. Application timelines have also been shortened to 90 days for drugs developed outside the country. For new drugs manufactured within India, the application will be reviewed within 30 days. A controversial clause which had stated that sponsors pay 60 per cent of the compensation prior the test has been scrapped and replaced with a legislation which now states that companies need to pay the total amount after it has been determined that the cause of death or injury occurred directly due to the CT.[9]

Impact of COVID-19

While COVID-19 has ravaged almost all countries and industries, the challenges the drug development and CT industry face are unique. Unlike others, it is imperative for researchers to continue with their work with minimal interruptions to come out with a safe vaccine and drug.

A drug development process of an experimental drug from molecule discovery to post-approval typically takes 7-9 years depending on nature of the disease, efficacy of the drug and prevalence amongst the patient population, with CTs alone taking at least 3-5 years before a drug is approved for release. This changes during an epidemic or a public health emergency. Given that the scope of enquiry is limited in the face of a pandemic, the question of maintaining a balance between providing wider and faster access of medicines to serious patients versus abandoning critical standard research procedures to develop a drug remains unanswered.

CTs during COVID-19

1) In United States

FDA, in response to COVID-19 has launched CTAP (Coronavirus Treatment Acceleration Program), a public private partnership for expediting the process of development of drug for COVID-19 by seeking help from its federal partners, industry and researchers to monitor changes in protocol and streamline efforts across institutions.

By cutting red tape and redeploying staff to evaluate proposals and provide regulatory advice as more and more institutes and scientists race to find a cure, FDA is trying to ensure medical access to sick patients at the earliest while maintaining safety of the drug. As on April 19, there were 72 CTs of potential therapies reported under FDA supervision.

The protocol applications upon receipt are triaged and forwarded to the FDA staff, who are required to respond within 24 hours. Further inputs and interactions are based on the scientific merit of the proposal, stage of development with ultra-rapid protocol review done in 24 hours.[11]

Emergency Use Authorisation

Apart from CTAP, FDA has certain provisions like Emergency Use Authorisation (EUA) that allows it to provide access to medical countermeasures (MCMs) that can be used to diagnose and treat a serious disease, especially during a public health emergency. The EUA programme was established in 2004 when the BioShield Act amended Section 564 of the Federal Food, Drug and Cosmetic Act to incorporate this legislation.[12]

For authorising an EUA, four statutory criteria should be met to ensure public health safety and care is on priority.

1. There must be a serious or life-threatening illness caused by a specified chemical, biological, radiological or nuclear agent.

2. It must be reasonable to believe that the product covered by the EUA is going to be effective for the intended use—diagnosing, treating or preventing either an illness or condition caused by a specific agent, or an illness or condition caused by an approved or authorised medical countermeasure deployed against the agent.

3. The known and potential benefits need to outweigh

11. FDA. Coronavirus Treatment Acceleration Program (CTAP). 2020. - https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap.
12. FDA Guidelines. - https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

the known and potential risks.

4. There must be no adequate, approved or alternative medical countermeasures available for the situation.

In 2009, in response to H1N1 flu, several drugs were authorised under EUA including an unapproved drug called Peramivir given the unmet medical need. While EUA is a necessary and timely tool for combating pandemics, pressing concerns about the side effects remain unanswered.[13]

Hydroxychloroquine Authorisation

On March 28, 2020 FDA issued an EUA to allow hydroxychloroquine (HCQ) sulfate and chloroquine phosphate products to be administered only to severe cases of COVID-19, keeping in mind the health risks. At the time of issuance, FDA was yet to conduct CTs on patients and EUA was issued on the basis of reports suggesting HCQ prevented the growth of the virus under laboratory conditions and that the condition of certain patients who received HCQ was improving. There is no information regarding the circumstances or of any other factors that might have led to the recovery. On April 24, 2020 FDA issued a warning against the use of HCQ outside clinical settings as data from CTs emerged that the drug does not reduce admission of patients to ICU, but on the contrary has been related to increased adverse events. On June 15, FDA revoked its EUA status to HCQ, hailed as a 'game changer' by the US President, after failing to establish potential benefits which can outweigh the risks.

The provision has come under the scanner given the circumstances under which the authorisation was made. While the legislation states that an EUA might be issued if there is reason to believe that the product might be effective and that the known potential benefits outweigh the risks, it is yet to be proven that HCQ satisfies both the conditions. EUAs are notorious for their lack of transparency as drug applications are not formally discussed and decisions are reviewed by a small team of FDA officials. Unlike FDA approvals, EUA can be cleared by FDA in as short as a couple of hours.

2) Worldwide

On March 20, 2020, the World Health Organization (WHO) announced a global Solidarity Trial in association with its members and partners to help find an effective treatment against COVID-19. The much-publicised trial will compare four treatment options against standard of care to assess their relative effectiveness against COVID-19 in 35 countries across 3500 patients including India. It will also help monitor and compare the disease progression and drug usage across countries ensuring constant communication throughout trials. One of the four treatment options is HCQ which has come under the scanner after a study in *Lancet* showed that the use of HCQ showed no evidence of benefits for COVID-19 patients, but saw increased risk of in-hospital death and heart rhythm problems. The influential study saw HCQ being banned across governments and the suspension of HCQ trials including the Solidarity Trial. But on June 5, 2020, *Lancet* retracted the study citing inability to conduct an independent audit of the data underlying the analysis and thus unable to vouch for the veracity of the study, which led to WHO resuming HCQ trials.

Given the criticality of CTs to finding a cure, it is natural for the researchers and academicians to rush to generate scientific evidence through medical studies. But the rate at which scientific research is being published stands at the risk of slipping through the rigorous peer review process, with healthcare experts and the public struggling to keep up. A recent study showing that medical journals publishing COVID studies have decreased their turnaround time by around 50 per cent with medical research still in preprint stage, reported by the media as concrete. While information dissemination is crucial and laudable in fighting the pandemic, questions regarding the quality and accuracy of the research come into play, especially given how studies in journals like *Lancet* wield influence over trials and policies across countries and consequently putting the lives of innumerous patients at risk. There is sadly not enough emphasis placed on the fallout of

13. *Medical Countermeasures Dispensing: Emergency Use Authorization and the Postal Model, Workshop Summary*. 2010. Washington, DC: National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK53122/#.

such carelessness in the midst of a highly politicised pandemic.

3) In India

In the memorandum dated March 20, 2020, the Department of Biotechnology in consultation with the DCGI has announced the expedition of CTs by fast-tracking the approval processes, reducing the timeline for each round of review and approval to 7–10 days. The DCGI has also sent a notice to all Pharmaceutical companies, granting speedy permissions for CTs, waiver/deferment of data submission for animal toxicity studies and stability study; and for emergencies, import licence will be granted without a registration certificate in the case of repurposed old drugs.[14] The Drug Rules and Drug Act do not contain any legal mechanism to expedite the process of review and approval for new drug development in the country.

Given the statement, there is a lack of clarity on the nature of waivers (which tests can be omitted, how much can be abbreviated and so on) and more concerning, the question of efficacy and safety for drugs developed in India. Repurposed drugs are slightly less prone to these concerns given data availability for animal toxicity and human CTs globally. However, DCGI must make sure that no drug may be approved without sufficient proof of clinical efficacy on the Indian patient pool.

In India, ICMR has issued a notification stating that the National Taskforce for COVID-19 recommends the use of HCQ for COVID-19 for asymptomatic healthcare workers involved with suspected or confirmed cases or asymptomatic household contacts of confirmed cases.[15] Following this directive, hospitals across India have prescribed HCQ for their medical workers leading to a shortage of the drug. But what was more alarming was that there was no scientific evidence backing the directive as well as the initial set of guidelines released on March 22 did not mention the side effects caused ranging from nausea to threatening conditions like hypoglycemia. Lack of informed consent on the part of ICMR has resulted in the drug being administered throughout the country, in some cases forced to be consumed by hospitals without being aware of the side effects. ICMR's own safety guideline 'National Ethical Guidelines for Biomedical Research in Human Participants' in 2017 states that any use of drugs during an outbreak must be accompanied by informed consent and subjected to review by the National Ethics Committee. This is particularly troubling given the political situation surrounding HCQ, when it is even more paramount that ICMR stick to its own guidelines. It also sets a precedent for other drugs like Remdesivir, which has been issued an EUA in the United States.

In May, ICMR based on emerging data and studies on HCQ continued to recommend the drug as a prophylactic for healthcare workers despite the abrupt reversal in the usage of HCQ in CTs globally. This was based on the case-controlled study which is soon to be published in the *Indian Journal of Medical Research* which states that four or more maintenance dosages of HCQ in healthcare workers were associated with significant decline in the chances of getting infected with COVID-19. A report on the ICMR study showcases that 50 per cent of those not on HCQ tested positive, 70 per cent of those on weekly dose of 400 mg HCQ tested positive, 40 per cent of those on 4–5 dosage over 3-week period tested positive while only 10 per cent of those on HCQ for a period of 6 weeks tested positive. Additionally, amongst health workers on HCQ alone, 49.4 per cent tested positive and of those not on HCQ, 53.3 per cent tested positive.[16] As the study is still in the pre-print stage, details on the impact of PPE or other compounding factors on the outcome are awaited, given there is no clarity yet if the combination of HCQ and PPE has resulted in disease reduction and if so, how much of it can be attributed to HCQ. ICMR's directive on May 22 to expand the prophylactic usage of HCQ to frontline workers deployed in containment zones and paramilitary personnel marks a big step given the number of people affected, and how scientific

14. https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTc2OQ.
15. https://www.icmr.gov.in/pdf/covid/techdoc/HCQ_Recommendation_22March_final_MM_V2.pdf.
16. Koshy, Jacob. 2020. "Coronavirus: Hydroxychloroquine with PPE Reduces Odds of COVID-19 in Health Workers: ICMR Researchers." *The Hindu*, June 1, 2020. https://www.thehindu.com/news/national/coronavirus-hydroxychloroquine-with-ppe-reduces-odds-of-covid-19-in-health-workers-icmr-researchers/article31724680.ece.

data backing the claim is yet to be verified.[17] Given the nature of an observational study, it is possible that this is an indication of correlation and does not necessarily imply causation. Only a randomised controlled trial in which one group is administered the drug and the other control group is given placebo can help evaluate the risk of contracting the disease.

It is equally important to differentiate between the use of HCQ as a prophylactic as recommended by ICMR and the use of it as treatment option in CTs. Globally, while HCQ is yet to provide any evidence of benefits in treating the moderately and severely affected, the in-vitro study of the drug showing antiviral efficacy and log reduction in viral RNA load of the virus is what has sparked interest in the first place. India is yet to administer CTs involving the efficacy of HCQ on patients infected by COVID-19, but reports indicate the usage of low doses of HCQ in mild to moderate patients across hospitals.

According to WHO's list of potential vaccines, there are 10 candidates in clinical development and 123 in the pre-clinical stage of development. The list also has Serum Institute of India, Zydus Cadila and Bharat Biotech from India amongst companies involved in developing a vaccine. The Health Ministry has stated that 4 out of 14 vaccine candidates from India are expected to enter the CT stage in 3–4 months and human CTs by the end of the year. While this timeline is much faster than the stipulated timeline of around 10 years, with the number of infections close to 7 lakh and fatalities touching 19,000 in the country, the government and Pharmaceutical firms are racing against time to develop a vaccine. In such a scenario, perhaps it is urgent now more than ever to ensure that a fine balance is met between speed and ensuring scientific standards, especially in the case of CTs, are rigorous, safe and worthy of public trust.

17. ICMR. 2020. Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for SARS-CoV-2 infection (in supersession of previous advisory dated 23rd March, 2020). https://www.icmr.gov.in/pdf/covid/techdoc/V5_Revised_advisory_on_the_use_of_HCQ_SARS_CoV2_infection.pdf.

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