COVID-19 Clinical Trials Report Card: Remdesivir

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Remdesivir is an antiviral drug, currently in development by the pharmaceutical company Gilead Sciences. It is thought that remdesivir may have a beneficial effect in treating patients with COVID-19, and the US FDA recently authorized emergency use of remdesivir [https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment] during the pandemic.

We have described the current research programme for remdesivir across all registered COVID-19 clinical trials.

What we did

We downloaded the ICTRP COVID-19 database [https://www.who.int/ictrp/en/] on 29 April 2020 and applied our data cleaning and extraction code for covid19.trialstracker.net [http://covid19.trialstracker.net] . Known cross-registrations are removed to avoid double-counting and fields are normalized to common terms (e.g. Phase II becomes Phase 2). For all current, planned, or completed studies in the final dataset (n=1760) we extracted all interventions explicitly mentioned in the relevant registry fields. For this report card, we included every trial that mentioned remdesivir as an intervention, and extracted key trial characteristics (blinding, randomization, study type, control type, dosage regimen, patient population, and sponsor).

We further examined the registry entry for each study to determine if remdesivir was the focus of the study, or if it was being used as a control, in combination with the active therapy of interest, or for other purposes.

We located 11 unique planned, current, or completed/suspended studies mentioning remdesivir as a treatment. Two are expanded access programs. Below we present a short description of the other nine studies and their designs, followed by a table with summary characteristics. Known cross-registrations for these trials are included in Table

1. We shall refer to the ClinicalTrials.gov registration for a given trial throughout the rest of the piece

Table 1: Cross-Registration and Location Details of Remdesivir Trials

Parent Registration	Other Registrations	Study Locations
NCT04315948	EUCTR2020-000936-23	France
NCT04280705	JPRN-jRCT2031190264	USA, Japan, South Korea, UK, Denmark, Greece, Germany, Singapore, Mexico, Spain
NCT04252664	None	China
NCT04257656	None	China
NCT04302766	None	No Country Given
NCT04292730	EUCTR2020-000842-32	USA, Japan, South Korea, UK, China, Iran, Switzerland, France, Germany, Hong Kong, Sweden, Netherlands, Singapore, Italy, Spain, Taiwan
NCT04292899	EUCTR2020-000841-15	USA, Japan, South Korea, UK, China, Switzerland, France, Germany, Hong Kong, Sweden, Netherlands, Singapore, Italy, Spain, Taiwan
NCT04323761	EUCTR2020-001453-49	USA, Belgium, UK, Switzerland, France, Germany, Netherlands, Italy, Israel, Spain
NCT04349410	None	USA
ISRCTN83971151	EUCTR2020-001366-11; NCT04330690; PER-010-20; IRCT20200405046953N1; NCT04321616; EUCTR2020-000982-18	South Africa, Switzerland, Thailand, Germany, Ireland, Norway, Israel, Canada, Brazil, India, Malaysia, Kenya, Peru, Saudi Arabia, Argentina,

		Lebanon, Italy, Honduras, Philippines, Indonesia, Qatar, Iran, Spain
IRCT20171122037571N2	None	Iran

Trials Sponsored by Gilead Sciences

Gilead currently sponsors two interventional clinical trials (NCT04292730 [https://clinicaltrials.gov/ct2/show/NCT04292730] , NCT04292899 [https://clinicaltrials.gov/ct2/show/NCT04292899]) and one expanded access (i.e. compassionate use) program (NCT04323761 [https://clinicaltrials.gov/ct2/show/NCT04323761]) for remdesivir in COVID-19.

The two randomized open-label trials are examining remdesivir, along with standard care, given as a loading dose followed by either 5 or 10 days of daily 100 mg infusions. This can then be followed by an additional "extension" treatment for 5-10 days. Both trials examine primary outcomes for efficacy (a 7-point scale for improvement) and a secondary outcome for "safety" (proportion of patients with adverse events).

- NCT04292730 [https://clinicaltrials.gov/ct2/show/NCT04292730] measures the primary outcome at day 11
- NCT04292899 [https://clinicaltrials.gov/ct2/show/NCT04292899] measures the primary outcome at day 14.

The most notable difference between the two trials is that NCT04292730 [https://clinicaltrials.gov/ct2/show/NCT04292730] has a "standard of care" control group that does not receive treatment with remdesivir, while NCT04292899 [https://clinicaltrials.gov/ct2/show/NCT04292899] is uncontrolled, even though it has a substantially higher enrolment target (6000 vs. 1600).

Government Sponsored Trials

USA

The US Government has registered one interventional trial for remdesivir in COVID-19 (NCT04280705 [https://clinicaltrials.gov/ct2/show/study/NCT04280705] , The AACT trial) through the National Institute for Allergy and Infectious Disease (NIAID) and an expanded access program (NCT04302766 [https://clinicaltrials.gov/ct2/show/NCT04302766]) administered by the US Army.

NCT04280705 [https://clinicaltrials.gov/ct2/show/study/NCT04280705] is a double-blind, randomised, placebo-controlled trial planned for 800 patients. Participants are given a 200 mg intravenous loading dose of remdesivir followed by up to 10 days of daily 100 mg intravenous maintenance doses. The original primary outcome was nearly equivalent to the outcome specified in the Gilead-sponsored trials (a 7-point scale for improvement assessed at 15 days).

Subsequently, an eighth category was added to the improvement scale. This outcome was then notably changed [https://clinicaltrials.gov/ct2/history/NCT04280705?A=14&B=15&C=merged#StudyPageTop] to a three-point scale, measuring time to recovery at 29 days. There are an additional 28 secondary endpoints in this study, including measurement of various biomarkers, tracking of adverse and serious adverse events, and other clinically relevant endpoints. While no complete results for this trial have been released to date, positive findings for the new primary endpoint were announced in a press release [https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19] after the product had been granted Emergency Use Authorization by the FDA.

France

The French Government, via their national institute of health research (INSERM), has registered an interventional clinical trial (NCT04315948 [https://clinicaltrials.gov/ct2/show/NCT04315948] , The DisCoVeRy Trial) that includes remdesivir alongside a number of other candidate treatments for COVID-19. Dosing is equivalent to the previously described studies (a 200 mg intravenous loading dose then up to 10 days of 100 mg daily intravenous maintenance doses). The primary outcome is a 7-point ordinal scale of intensity of disease, as measured at 15 days, with 28 secondary or "other" outcomes measuring a range of clinical endpoints and biomarkers. Participants in this study receive either remdesivir, lopinavir/ritonavir with interferon beta-1a, lopinavir/ritonavir without interferon beta-1a, or hydroxychloroquine, in addition to standard care, or standard care alone. The trial is open-label and plans to enrol 3100 participants.

World Health Organization

The World Health Organization is sponsoring The SOLIDARITY Trial, a global trial of various proposed treatments for COVID-19. The overall trial is registered as ISRCTN83971151 [http://www.isrctn.com/ISRCTN83971151] with a number of additional country-specific registrations (see Table 1).

Participants are randomized to receive either remdesivir, chloroquine or hydroxychloroquine, or lopinavir/ritonavir with or without interferon beta. There is no masking. The ISRCTN entry does not specify dosing; however, the additional registrations suggest that the standard regimen of 10 days (200 mg intravenous loading + 100 mg/day maintenance) is being used. No enrolment target is specified for this trial; however, it is expected to be "several thousand" across all global trial sites. The ICTRP record estimates 10,000. All-cause mortality, stratified by disease severity is the primary outcome and duration of hospital stay and time to ventilation are the secondary outcomes.

Academic Trials

Two similar protocols examining remdesivir for COVID have been registered by Capital Medical University (NCT04252664 [https://clinicaltrials.gov/ct2/show/NCT04252664] , NCT04257656 [https://clinicaltrials.gov/ct2/show/NCT04257656]). Neither trial is currently recruiting. Both trials were planned to be randomized, masked, and placebo controlled, using the standard dosing regimen over 10 days or until discharge. The main difference between the two trials was the study population (mild to moderate COVID in NCT04252664

[https://clinicaltrials.gov/ct2/show/NCT04252664] and severe COVID in NCT04257656 [https://clinicaltrials.gov/ct2/show/NCT04257656]) and slightly different outcomes. In NCT04252664 [https://clinicaltrials.gov/ct2/show/NCT04252664] , the primary outcome was time to recovery, while NCT04257656 [https://clinicaltrials.gov/ct2/show/NCT04257656] examined time to clinical improvement. Both studies had 10 secondary outcomes with some differences between the two.

NCT04257656 [https://clinicaltrials.gov/ct2/show/NCT04257656] was officially terminated early, after enrolling 237 participants, owing to a lack of patients as China's outbreak came under control. The results of NCT04257656 [https://clinicaltrials.gov/ct2/show/NCT04257656] trial were published in The Lancet [https://doi.org/10.1016/S0140-6736(20)31022-9] and showed that "remdesivir was not associated with statistically significant clinical benefits."

NCT04252664 [https://clinicaltrials.gov/ct2/show/NCT04252664] , however, is currently listed as "Suspended," also owing to lack of patients. It is unclear why this trial was "suspended" instead of terminated, and why it was not reported like NCT04257656 [https://clinicaltrials.gov/ct2/show/NCT04257656] . It was expected to enroll 308 participants.

The Tehran University of Medical Sciences has registered a single-arm, uncontrolled, open-label trial of remdesivir for COVID-19 (IRCT20171122037571N2 [https://en.irct.ir/trial/46660]). The trial measures both time to clinical improvement and recovery as primary endpoints and five secondary outcomes, including mortality and safety measures. The target sample size is 120 participants.

Other trials

We located one additional unique trial registration that included remdesivir as a treatment (NCT04349410 [https://clinicaltrials.gov/ct2/show/NCT04349410]). The trial is sponsored by The Camelot Foundation and uses a proprietary method for measuring "change in tissue resulting from inter alia a disease process. This includes inter alia coronary artery disease (CAD), cancer and infectious/inflammatory processes including CoVid-19 pneumonia (CVP) resulting from the metabolic and regional blood flow differences (RBFDs) caused by these diseases." Currently the treatment has 11 arms using a variety of potential treatments for COVID-19, including remdesivir. It is planning to randomize 500 participants to the 11 arms, with no control. Only the investigator is blinded to the study condition. Improvement on the proprietary scale at 3 days is the primary outcome of the study. Ventilation status and survival are secondary outcomes.

Summary

Table 2 includes the overall characteristics of all interventional remdesivir trials (excluding the two "Expanded Access" registrations).

Table 2: Overall Characteristics of Registered Remdesivir Trials

Total Registrations	9
Planned Enrollment	22,437
Randomized	8
Blinded	4

Control Type	
Placebo	3
“Standard of Care”	3
Uncontrolled	3

Assessment of the research landscape of remdesivir for COVID-19 shows some strengths and some weaknesses.

The trials are universally aligned on the dosing of remdesivir and many are using similar primary outcome scales. However, the recent changes to the NIAID trial outcomes, moving away from the 7-point scale, which includes outcomes such as death and ventilation, and moving towards time to recovery, with a smaller 3-point scale assessed over a longer time frame, compromises this comparability. Given that investigators claim this outcome definition and duration was changed based on additional information about the disease, this may infer existing outcome sets are not well suited to what we now know about the disease course and confuse outcome selection and synthesis of common outcomes moving forward. Less than half of the trials are blinded and a third are uncontrolled. Gilead is currently running the largest trial focused solely on remdesivir (n=6000), but without a control group. Of the three trials that meet the highest design standard (randomized, masked, and placebo controlled) none has successfully reached completion.

The Chinese studies from Capital Medical University have both halted, one permanently and one apparently temporarily, owing to lack of COVID-19 patients. The third, the NIAID study, will begin offering patients on placebo the chance to switch to remdesivir based on the interim findings, according to Dr. Anthony Fauci [https://www.washingtonpost.com/business/2020/04/29/gilead-says-positive-results-coronavirus-drug-remdesivir-will-be-released-by-nih/] . Given the results to date, additional well-designed studies will be necessary to bolster the evidence for using remdesivir in patients with COVID-19. Trials lacking a control are unlikely to add substantially to evidence for the efficacy of remdesivir in this context.

Note: This work has not been peer-reviewed and the data is preliminary. We hope to continue to improve, expand, and update the data on trials of these and other drugs in the near future.

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NHS research. Henry co-founded the COMPare [https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3173-2] project, which monitored outcome switching in 5 major medical journals.
COI: HMD has been employed on grants from the Laura and John Arnold Foundation.

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