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HEALTH

# Hundreds Receive Plasma From Recovered Coronavirus Patients in National Study

Researchers seek evidence about plasma therapy outcomes and new knowledge for future outbreaks

Melissa Cruz, an emergency room technician in Renton, Wash., who had Covid-19, donated plasma on April 17.

PHOTO: LINDSEY WASSON/REUTERS

*By Amy Dockser Marcus*

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Six hundred severely ill Covid-19 patients have received blood plasma from recovered patients in a study researchers hope sheds light on whether the experimental therapy improves health outcomes and yields other useful data outside the scientific rigor of a traditional clinical trial.

The patients are participating in a national expanded-access program authorized in early April by the federal Food and Drug Administration. Expanded access, also known as compassionate use, is often sought by patients with life-threatening illnesses for which there are no approved

therapies, or who can't participate in clinical trials.

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The utility of data from compassionate-use studies is a source of debate within the medical and scientific community, where the gold standard for determining a new drug's safety and efficacy has long been the controlled clinical trial. In those traditional randomized trials, one group of patients gets the experimental drug and a control group gets either the standard therapy or a placebo.



Critics say it is impossible for compassionate-use studies to show whether a drug is working, because every patient in those studies gets the compound, with no control group for comparison. Opponents also worry that patients could become reluctant to enroll in traditional clinical trials for fear they won't get the experimental therapy.

Without a control group, though, researchers can't be certain what is making the difference. Age, gender, weight, underlying health conditions, socioeconomic status and doctors' own biases all can influence a patient's outcome. And in many diseases, including Covid-19, some patients are going to get better on their own. As a result, compassionate use has been viewed as a way to give patients emergency access to experimental therapies rather than a source of reliable data.

"Will expanded access give us the same data as a perfect randomized, controlled trial? No," said Michael Joyner of the Mayo Clinic in Rochester, Minn., and principal investigator of the expanded-access convalescent plasma project. "Will we gain insight under unusual circumstances? Yes."

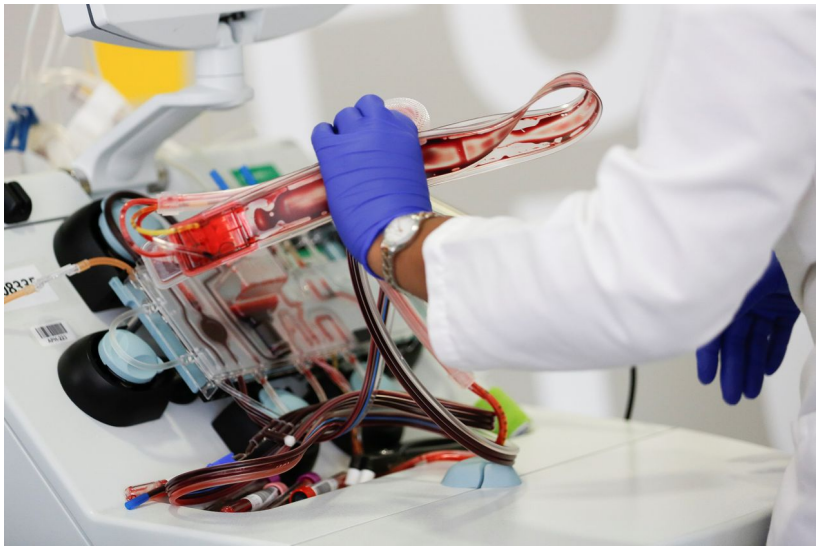
As of Sunday, the University Hospital in Madison, Wis., part of UW Health, had transfused 11

Covid patients with convalescent plasma under the expanded-access protocol, said William Hartman, an anesthesiologist and one of the investigators on the study. Eight of the patients were in life-threatening situations and now are in various stages of recovery, he said. The other three received plasma before or just after admission to the intensive-care unit and have shown improvement: One was discharged from the hospital; one was taken off a ventilator within a day and symptoms have improved. The third hasn't worsened and hasn't required ICU admission, he said.

"There is no lab test that proves convalescent plasma caused these results," Dr. Hartman said. "Based on when we gave them the transfusion and the outcomes, we are encouraged."

Between 5,000 and 10,000 people may ultimately be eligible to enroll in the convalescent plasma program, the Mayo Clinic's Dr. Joyner said. Investigators will compare patients who get the plasma with similar patients who didn't receive it, such as very ill patients at a hospital where the therapy wasn't available. Researchers hope the knowledge they gather can inform future trials and aid doctors and researchers in another outbreak.

Another analysis of compassionate-use data, about the experimental drug remdesivir from Gilead Sciences Inc. published in the New England Journal of Medicine, came under criticism. Scientists pointed out that the Covid-19 patients received the drug in centers around the world where care may have differed, data on some patients was incomplete and there was no comparison group.



A phlebotomist processes a convalescent plasma donation at the Central Seattle Donor Center of Bloodworks Northwest on April 17.

PHOTO: LINDSEY WASSON/REUTERS

That study's first author, Jonathan Grein, of Cedars-Sinai Medical Center in Los Angeles, said given how little is known about the coronavirus and how to treat it, "I think at this point any information is potentially helpful." He said the study, funded by Gilead Sciences, noted the findings were limited and preliminary. "It is a starting point, an opportunity to aggregate our initial experiences," he said.

There also are traditional randomized controlled studies of remdesivir under way.

The FDA has shown flexibility in accepting expanded-access data during the drug-approval process, particularly for rare conditions. The FDA also has worked closely with companies trying to extract "real world evidence" about patients' experiences with new or experimental drugs from sources such as electronic health records.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Convalescent plasma has been tried as a potential intervention in previous public-health emergencies, including for Ebola and severe acute respiratory syndrome (SARS), according to H. Clifford Lane, clinical director at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. But because robust randomized clinical trials weren't conducted, "there is still no clear data to support that it has been of benefit."

Even with the added rigor, Dr. Lane said it would be difficult to tell whether plasma therapy or something else is responsible for any possible improvement in the Covid-19 patients. "Maybe the patients improved because as doctors got more practice treating Covid patients they did a better job, and not because the intervention had an effect," he said. In the end, "thousands of anecdotes are still just thousands of anecdotes."

Dr. Lane said the NIH is involved in efforts to launch randomized controlled clinical trials of manufactured intravenous immunoglobulin containing antibodies prepared from the serum of many recovered Covid patients.

Holly Fernandez Lynch, an assistant professor of medical ethics at the University of Pennsylvania, said she supports trying to glean as much information as possible from the use of experimental therapies. Nonetheless, since very little is yet known about the coronavirus itself, patient outcomes will be even more difficult to analyze compared with better-understood diseases.



"There is a sense of emergency and feeling we don't have time to get answers," she said. "If we keep acting like we can't study the interventions, then we will be in the same position next time and still not know how to effectively treat people."

Still, the compassionate-use data on plasma therapy may help shape future studies. Peter Marks, director of the FDA Center for Biologics Evaluation and Research, said, "They may get a readout on some questions sooner than we would have, had this been a conventional trial."

Other randomized controlled trials in the works include one to test convalescent plasma given prophylactically to those at risk of Covid-19 infection, says Shmuel Shoham of Johns Hopkins University School of Medicine, the principal investigator on that trial. With Covid-19, there is room for both broad access to experimental therapies and controlled trials, he said. "There are enough questions that are worth investigating, and sadly a lot of patients."

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