Recruitment Strategy for Potential COVID-19 Convalescent Plasma Donors

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Coronavirus disease 2019 (COVID-19) represents a pandemic and global health crisis. In the first wave of the disease in the United States, COVID-19 was diagnosed in approximately 2 million individuals and contributed to more than 100,000 deaths.[1] The number of COVID-19 diagnoses and related deaths are anticipated to perpetuate in subsequent waves of the disease.[2] The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which causes COVID-19 appears to be a new human pathogen with limited efficacious treatments including the antiviral remdesivir and the glucocorticoid dexamethasone.[3,4] However, there is robust historical precedent to anticipate that human convalescent plasma is a viable option for mitigation and treatment of COVID-19.[5,6] Human convalescent plasma leverages the antibody response of a recently sick and recovered COVID-19 patient as a plasma donor.[7] The donated plasma, which is rich in neutralizing antibodies to the SARS-CoV-2 virus, is transfused to a currently sick COVID-19 patient to mitigate ongoing symptomology and induce passive immunity.[7] Thus, the US Food and Drug Administration (FDA) in collaboration with Mayo Clinic and national blood banking community developed a national Expanded Access Program to collect and distribute convalescent plasma donated by COVID-19 survivors.[8] Theoretically, within 4 to 6 weeks of the onset of the US COVID-19 outbreak, human convalescent plasma should have been readily available due to the existing plasma collection infrastructure within the blood banking community[9] and the large numbers of COVID-19 survivors who could have donated high-titer immunoglobulin-containing plasma.[10] However, logistical issues produced a convalescent plasma fulfillment gap that created an urgent need to develop strategies to recruit eligible donors at national, regional, and local blood centers. Thus, the present narrative overviews the strategy developed by our team to identify and recruit COVID-19 survivors to donate convalescent plasma at the Mayo Clinic Blood Donor Center in Rochester, Minnesota.

Emerging data from the COVID-19 pandemic support the use of convalescent plasma therapy. There is evidence to suggest that SARS-CoV-2 elicits a robust immune response with high levels of antibodies and immunoglobulins (M and G) between 11 and 21 days after the onset of COVID-19, suggesting a relatively large window of time and high probability of successful extraction of high-titer anti−SARS-CoV-2 plasma from donors.[10] Consistent with this observation, convalescent plasma−treated COVID-19 patients had large reductions in serum SARS-CoV-2 serum viral loads after convalescent plasma infusion, suggesting a viral neutralizing effect of the anti−SARS-CoV-2 antibodies.[11] Some theoretical concerns for the use of convalescent plasma therapy for COVID-19 have been raised,

including the risk of transfusion-related lung injury, transfusion-related circulatory overload, and antibody-dependent enhancement of COVID-19.[12] However, in a large study of 20,000 patients transfused with convalescent plasma, there was no signal of toxicity beyond what is expected from plasma use in severely ill patients.[8,13] Although the efficacy of convalescent plasma remains unknown, preliminary investigations have provided a signal of possible benefit in severely ill COVID-19 patients.[14,15] Thus, recruitment of COVID-19 survivors was fundamental to meet the rapidly growing demand for convalescent plasma as the pandemic progressed and clinical interest in convalescent plasma therapy increased.

Recruitment of convalescent plasma donations at the Mayo Clinic Blood Donor Center in Rochester, Minnesota, required a strategy to interface with the community of recovering COVID-19 patients and recruit eligible convalescent plasma donors. To accommodate the growing magnitude and geographical spread of COVID-19 survivors and the changing convalescent donor eligibility criteria outlined by regulatory agencies and local institutions, we required this strategy to be inherently modifiable. Overall, this recruitment strategy used a simple survey, an algorithm for triaging donors, a workflow for connecting donors with Mayo Clinic Blood Donor Center, a team of physician navigators (including medical students) to screen eligible donors, and a support center for donor questions. This strategy may be adopted by other institutions to rapidly increase convalescent plasma donor recruitment.

DONOR RECRUITMENT STRATEGY OVERVIEW

To identify previously ill recovered COVID-19 survivors who satisfied present and changing eligibility criteria to donate convalescent plasma, we used a brief online survey hosted by the Research Electronic Data Capture system.[16,17] To reduce user time-burden, this survey was limited only to questions deemed necessary to determine donor eligibility and to maximize the retention of interested volunteers (Table). Although the eligibility criteria for convalescent plasma donation changed with the development of COVID-19 laboratory tests and greater understanding of SARS-CoV-2 transmission,[9,18] at the time of writing, three key survey questions identified eligible convalescent plasma donors: 1) Did you test positive for COVID-19 (via nasopharyngeal swab or serological test)? (Question 8); 2) Are you still symptomatic for COVID-19? If no, when did your symptoms resolve? (Question 10); and 3) Where is your current residence (city and state)? (Question 7).

The Web-based donor recruitment survey was distributed to potential convalescent plasma donors via several avenues. The link to the recruitment survey and service center email address was displayed to all Mayo Clinic staff on the Mayo Clinic internal homepage, as well as the Mayo Clinic Blood Donor Center website. The link to the survey was provided to a network of collaborating physicians (including infectious disease and community internal medicine physicians)

TABLE. Convalescent Plasma Donor Recruitment Survey Questions[a]

1.	Do you authorize that the information you enter in this form can be shared with Mayo Clinic?
2.	Do you authorize Mayo Clinic staff to contact you by phone and/or e-mail?
3.	What is your first and last name?
4.	What is your date of birth?
5.	What is the best e-mail address to reach you?
6.	What is the best phone number to reach you?
7.	Where is your current residence (city and state)?
8.	Did you test positive for COVID-19 (nasopharyngeal swab or serological test)?
	What was the date of your positive test result?[b]
	Was this test result processed through the Mayo Clinic Health System?[b]
9.	When did your symptoms start?
10.	Are you still symptomatic for COVID-19?
	When did your symptoms resolve?[c]
11.	Have you ever donated blood and/or plasma?
12.	If you meet the eligibility criteria, would you be interested in donating your plasma?

[a]COVID-19 = coronavirus disease 2019.
[b]Presented if respondent answered "yes" to question 8.
[c]Presented if respondent answered "no" to question 10.

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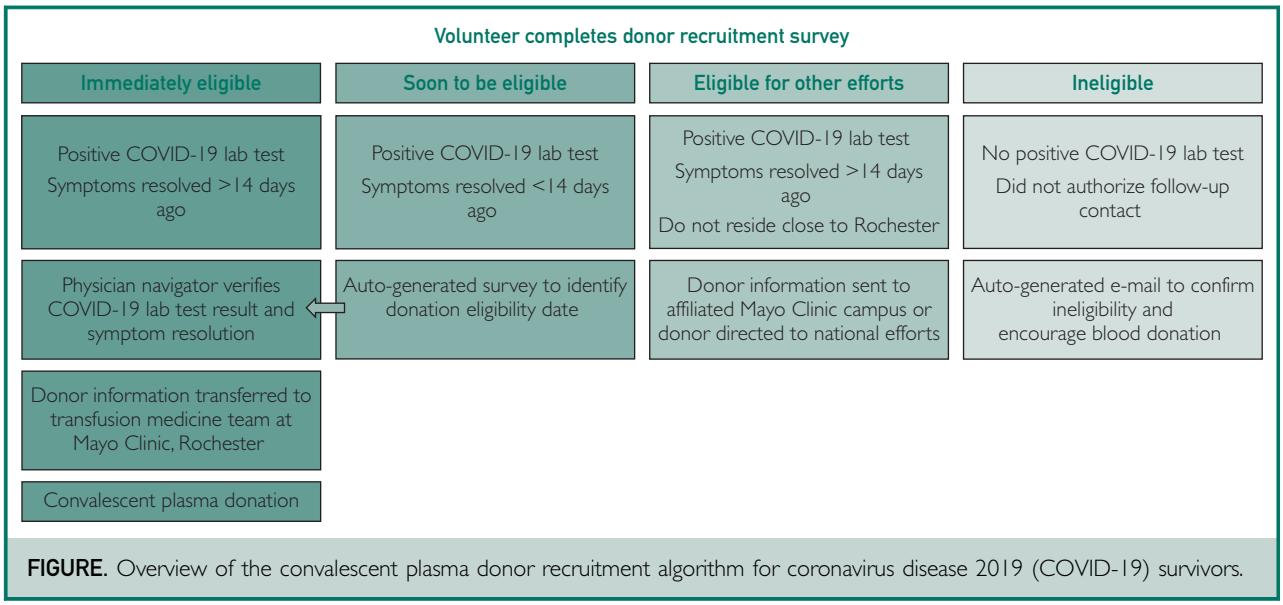

FIGURE. Overview of the convalescent plasma donor recruitment algorithm for coronavirus disease 2019 (COVID-19) survivors.

and health care providers within the Mayo Clinic system responsible for monitoring the recovery and quarantine of COVID-19 survivors who could send the link to interested COVID-19 patients. Also, the electronic recruitment survey was distributed to local and state health departments and broadcast directly to potential donors via social media platforms. Local convalescent donor recruitment efforts were also supplemented by national plasma donor recruitment campaigns that commenced later in the pandemic (eg, "The Fight Is in Us"[19]).

All procedures accessed public information and did not require ethical review as determined by the Mayo Clinic Institutional Review Board in accordance with the Code of Federal Regulations, 45 CFR 46.102, and the Declaration of Helsinki. All survey responses were stored in a secure database that enabled donor triaging. We maintained physical, electronic, and procedural safeguards to prevent unauthorized access to and improper use of personal information. All personal information voluntarily provided by prospective donors was transmitted via a secure encrypted connection and stored within the Mayo Clinic Research Electronic Data Capture database that resides behind multiple layers of security. The contact information for volunteers reporting a residence in Arizona and Florida was transferred to a collaborator at the appropriate Mayo Clinic campus via the secure and encrypted Mayo Clinic system.

As outlined in the following discourse, responses to the three key questions delineated contact priority and enabled our team to classify respondents as: 1) an immediately eligible convalescent plasma donor, 2) a soon-to-be-eligible convalescent plasma donor, 3) eligible for other convalescent plasma donation efforts, and 4) ineligible to donate convalescent plasma (Figure).

Immediately Eligible Convalescent Plasma Donors

Volunteers were deemed immediately eligible for convalescent plasma donation if they reported: 1) a positive COVID-19 laboratory test via a positive polymerase chain reaction (PCR) or serological test, 2) being asymptomatic for COVID-19 for 14 days or more, and 3) currently residing within close proximity to the Mayo Clinic Rochester, Minnesota, campus (Figure).[18] Potentially eligible donors were then contacted by our team of physician navigators to confirm survey responses, including COVID-19 laboratory test results and symptom resolution.

For the subset of potential donors that obtained COVID-19 testing through the Mayo Clinic system, with the authorization of the potential donor (Table), physician navigators accessed the individual's electronic medical records to view only relevant health information including confirming test results and dates. Physician navigators were familiar with the Mayo Clinic electronic health records and could rapidly identify information concerning a potential donor's testing and medical care related to COVID-19. Potential donors who obtained COVID-19 testing through an external health system were asked to securely send a copy of their test results to the physician navigator team for review. With verbal authorization from the potential donor, physician navigators sent contact information and test results to the Mayo Clinic Rochester Blood Donor Center team.

Next, eligible donors were contacted by a transfusion medicine team member to review basic background information for a blood product donation and schedule an appointment for donation. To ensure donors could easily navigate newly established health screening checkpoints at Mayo Clinic entrances, a letter was provided to each donor outlining their reason for entering the facility despite a recent COVID-19 infection. On the day of plasma donation, donors were required to successfully complete the standard blood donation in-person questionnaire and screening exam. Following donation, plasma underwent standard infectious agent testing and SARS-CoV-2 enzyme-linked immunosorbent assay. Convalescent plasma donors with SARS-CoV-2 plasma antibody titers greater than or equal to 160 and satisfactory blood product screening (eg, negative for human leukocyte antibody) could be contacted 28 days following the initial donation to schedule a second plasma donation.[18]

Soon-to-Be-Eligible Convalescent Plasma Donors

Volunteers were deemed soon-to-be-eligible convalescent plasma donors if they reported: 1) a positive COVID-19 laboratory test via a PCR or serological test, and 2) being asymptomatic for COVID-19 for less than 14 days (Figure).[18] Upon survey submission, soon-to-be-eligible donors received an automated email indicating that our team would contact them 14 days after their reported date of symptom resolution. Coronavirus disease 2019 survivors who reported a positive COVID-19 laboratory test and remained symptomatic for COVID-19 received a similar automatically generated email providing them with a link to a supplemental survey that captured the date of becoming COVID-19 symptom free. Once COVID-19 survivors became COVID-19 symptom free for 14 days or more, they were reclassified as immediately eligible for convalescent plasma donation and contacted by our physician navigator team for verification of test results and symptomology.

Convalescent Plasma Donors Eligible for Other Efforts

Regardless of their COVID-19 symptom status, potential donors were deemed to be eligible for other efforts beyond convalescent plasma donation at the Mayo Clinic Blood Donor Center in Rochester, Minnesota, if they reported: 1) a positive COVID-19 laboratory test via a PCR or serological test, and 2) a current residence beyond a reasonable distance from Mayo Clinic Rochester (Figure). If a respondent reported current residence in close proximity to Mayo Clinic campuses in Florida or Arizona, their contact information was transferred to a collaborator at the appropriate campus. Alternatively, respondents who were not in close proximity to any Mayo Clinic campus were provided information about national initiatives that were encouraging convalescent plasma donation and could direct a large volume of potential donors, including the National Convalescent Plasma Project,[20] the American Association of Blood Banks COVID-19 website,[21] and "The Fight Is in Us."[19]

Ineligible Convalescent Plasma Donors

Respondents were deemed ineligible to donate convalescent plasma and were immediately excluded from follow-up by our team

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if they 1) reported no positive COVID-19 laboratory test, 2) submitted an incomplete survey, 3) did not authorize follow-up contact by our team, or 4) could not be contacted by our team for follow-up (Figure). Volunteers were also excluded from follow-up by our team if they declined contact authorization at any time. Ineligible respondents received an automated email to communicate both our gratitude and the reason for their ineligibility. This automated email also included a new call to action for interested volunteers — we encouraged the individuals (if eligible) to perform a standard blood donation to prevent future blood shortages and direct them to the American Association of Blood Banks website (http://covidplasma.org/) which provides blood donation information.[21] Also, our donor service center encouraged interested potential donors who reported COVID-19 symptoms but did not receive a COVID-19 clinical test to contact their health care provider for a serology test and then fill out the recruitment survey again if they were seropositive.

CONVALESCENT PLASMA DONOR SERVICE CENTER

Our Web-based recruitment survey and all e-mail communications to interested potential donors contained the e-mail address for our convalescent plasma service center. The service center team used available resources from the US FDA, Mayo Clinic, and the blood banking community to support questions regarding donor eligibility and COVID-19 testing.[9,18] Also, the service center supported the physician navigator team by providing ongoing communication with screened eligible donors.

STRENGTHS OF THE RECRUITMENT STRATEGY

This convalescent plasma donor recruitment strategy had several key strengths:

1) The recruitment strategy had inherent scalability to meet the growing magnitude of recovering COVID-19 patients and enabled filtering by donor location to link the volunteer to a convenient donation center.
2) This strategy reduced the administrative and clinical workload associated with screening potential convalescent plasma donors experienced by transfusion staff at the Mayo Clinic Blood Donor Center. Thus, the blood donation team was able to continue collecting apheresis platelet, platelets, and whole blood donations while also scaling up convalescent plasma donations during the ongoing pandemic.
3) The simple Web-based screening survey optimized volunteer convenience and the screening algorithm enabled rapid identification of currently eligible volunteers, retained interested volunteers who were not eligible upon initial survey completion, and provided a new call to action to perform a standard blood donation, if eligible, for those who did not meet convalescent plasma donation eligibility criteria.
4) This recruitment approach accommodated real-time modifications to the US FDA[18] and Mayo Clinic Blood Donor Center convalescent plasma donor eligibility criteria. For example, when serologic testing was recognized as a confirmatory test for COVID-19, we modified our screening algorithm and automatically contacted volunteers who had previously met or had greater likelihood of meeting eligibility criteria.[18]
5) This recruitment strategy was comprised by a team of physician navigators (including medical students), researchers, and technicians who collaborated with transfusion medicine personnel at Mayo Clinic. Our team provided a full-service interface for the community of COVID-19 survivors that identified eligible donors and educated interested volunteers regarding COVID-19 laboratory testing and convalescent plasma donation information using current federal- and state-level guidelines. Notably, beyond requiring a fundamental understanding of COVID-19 symptomology and testing, plasma donation, and how to navigate electronic health records (physician

navigators), this program did not require specialized training which means it may be implemented by other institutions.

FUTURE CHALLENGES AND PERSPECTIVES

Our strategy for interfacing with the community of COVID-19 survivors may be expanded through the following avenues:

1) By introducing plasma fractionators into our recruitment network, we may recruit donors to contribute to a hyperimmune immunoglobulin G product for COVID-19. Two important populations of eligible donors would be immediate candidates for the plasma fractionation route: a) individuals who have antibody titers below the threshold thought to be efficacious for COVID-19 treatment, and b) volunteers ineligible for standard blood donation, such as multiparous women with human leukocyte antigen antibodies.
2) There is the opportunity to leverage electronic medical records to, upon a positive COVID-19 test result, automatically alert the ordering physician to provide the patient with the link to our donor recruitment survey and support center email address. As the availability of serologic tests increases, this avenue will enhance the volume of donors that did not receive an initial diagnostic test.
3) Partnership with external health care systems or institutions using this recruitment strategy will increase both the number of potential plasma donors and enhance donation convenience for potential donors. Currently, our strategy encourages COVID-19 survivors to donate at the Mayo Clinic Blood Donor Center in Rochester, Minnesota. By partnering with other health systems we may sort eligible donors by current residence and direct volunteers to the closest donation center. As post-secondary campuses re-open, institutions may broadcast this convalescent plasma donor recruitment survey to previously ill recovered students, staff, and faculty.

CONCLUSION

In response to the COVID-19 pandemic, the US FDA, in collaboration with Mayo Clinic and the national blood banking community, developed a national Expanded Access Program to collect and distribute convalescent plasma donated by COVID-19 survivors.[8] However, at the onset of the US COVID-19 outbreak, multiple logistical hurdles prevented a satisfactory supply of convalescent plasma.[9] To overcome the convalescent plasma fulfillment gap, our team of researchers and physicians developed a strategy to identify and recruit COVID-19 survivors to donate convalescent plasma at the Mayo Clinic Blood Donor Center in Rochester, Minnesota. This recruitment strategy used a simple Web-based survey, an algorithm for triaging donors, a pipeline for connecting donors with Mayo Clinic blood transfusion centers, a team of experts to screen eligible donors, and a support center for donor questions. By partnering with external health care systems and post-secondary institutions to distribute our recruitment survey, or with plasma fractionators to collect plasma from individuals who are deemed ineligible for convalescent plasma donation by blood banks, we may continue to grow the volume of convalescent plasma for the treatment of COVID-19.

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Abbreviations and Acronyms: **COVID-19** = coronavirus disease 2019; **PCR** = polymerase chain reaction; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus-2; **US FDA** = US Food and Drug Administration

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REFERENCES

1. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): cases in the US. Published 2020. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed June 7, 2020.
2. USA Facts. Coronavirus Locations: COVID-19 Map by County and State. Published 2020. https://usafacts.org/visualizations/coronavirus-covid-19-spread-map/. Accessed July 15, 2020.
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—preliminary report. *N Engl J Med*. 2020.
4. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2020.
5. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med*. 2006;145(8):599-609.
6. Casadevall A, Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. *Clin Infect Dis*. 1995;21(1):150-161.
7. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. *J Clin Invest*. 2020;130(4):1545-1548.
8. Joyner M, Wright RS, Fairweather D, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. *J Clin Invest*. 2020.
9. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest*. 2020;130(6):2757-2765.
10. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clin Infect Dis*. 2020.
11. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA*. 2020;323(16):1582-1589.
12. Dzik S. COVID-19 Convalescent plasma: now is the time for better science. *Transfus Med Rev*. 2020;34(3):141-144.
13. Joyner MJ, Bruno K, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc*. 2020;95(9):1888-1897.
14. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA*. 2020;324(5):460-470.
15. Liu STH, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a matched control study. *medRxiv*. 2020.
16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
17. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
18. US Food and Drug Administration. Recommendations for Investigational COVID-19 Convalescent Plasma. Published 2020. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Accessed July 15, 2020.
19. The Fight Is in Us. https://thefightisinus.org/. Accessed July 15, 2020.
20. National Convalescent Plasma Project. https://ccpp19.org/donors/index.html. Accessed July 15, 2020.
21. The American Association of Blood Banks (AABB). COVID-19 website. http://covidplasma.org/. Accessed July 15, 2020.