

ORIGINAL ARTICLE

Early and out-of-hospital use of COVID-19 convalescent plasma: An international assessment of utilization and feasibility

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Abstract

Background and Objectives: The use of coronavirus disease 2019 (COVID-19) convalescent plasma (CCP) in the treatment of patients with severe acute respiratory syndrome-2 infection has been controversial. Early administration of CCP before hospital admission offers a potential advantage. This manuscript summarizes current trials of early use of CCP and explores the feasibility of this approach in different countries.

Materials and Methods: A questionnaire was distributed to the International Society of Blood Transfusion (ISBT) CCP working group. We recorded respondents' input on existing trials on early/outpatient CCP and out-of-hospital (OOH)/home transfusion (HT) practices in their countries and feedback on challenges in initiating home CCP infusion programmes. In addition, details of existing trials registered on *clinicaltrials.gov* were summarized.

Results: A total of 31 country representatives participated. Early/OOH CCP transfusion studies were reported in the United States, the Netherlands, Spain and Brazil. There were a total of six published and five ongoing trials on the prophylactic and therapeutic early use of CCP. HT was practised in Australia, the UK, Belgium, France, Japan, Nigeria, the Netherlands, Spain, Italy, Norway, the United States and some provinces in Canada. Thirty-four representatives indicated a lack of OOH CCP or HT in their institutions and countries. Barriers to implementation of OOH/HT included existing legislation, lack of policies pertaining to outpatient transfusion, and associated logistical challenges, including lack of staffing and resources.

Conclusion: Early administration of CCP remains a potential option in COVID-19 management in countries with existing OOH/HT programmes. Legislation and regulatory bodies should consider OOH/HT practice for transfusion in future pandemics.

KEYWORDS

convalescent plasma, COVID-19, home transfusion

Highlights

- Data on the benefit of early administration of COVID-19 convalescent plasma (CCP) are emerging.
- Out-of-hospital CCP administration is associated with different logistic challenges that need to be taken into account by institutions/facilities that are considering the implementation of this practice.

INTRODUCTION

Transfusion of convalescent plasma from recovered individuals has been tried as a therapeutic approach in multiple epidemics and pandemics of novel pathogens [1]. In the context of the coronavirus disease 2019 (COVID-19) pandemic, while vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were awaiting development, testing and deployment, COVID-19 convalescent plasma (CCP), hyperimmune globulins, and antiviral monoclonal antibodies each offered an attractive and feasible option for passive immunization.

COVID-19 convalescent plasma offers a readily available therapy to provide neutralizing antibodies for COVID-19-infected patients and via other mechanisms – for example, via modifying inflammatory markers [2]. Multiple clinical trials have studied the effectiveness of CCP administration in unselected hospitalized patients with moderate to severe COVID-19; overall, these trials have not demonstrated a benefit of CCP on all-cause mortality, progression of the disease or hospital stay [3–5]. The published trials have shown contradictory findings, likely in part due to heterogeneity in regard to the timing, dose or content of CCP administered, or severity of the infection

[4–6]. No benefit has been demonstrated in unselected subgroups of hospitalized patients; however, some studies do indeed suggest efficacy in subgroups who have surrogate characteristics for the probable lack of endogenous neutralizing antibodies. CCP is most likely to be effective if administered early in the disease, before the patient's own antibody response, in particular, in patients who cannot mount their own immune response, such as the immunocompromised or immune deficient patients [7, 8]. Early administration is also believed to prevent innate immune cell migration and avoid lung damage [9]. CCP effectiveness could also be influenced by anti-SARS-CoV-2 antibody titres in the recipients before administration [2].

Research to evaluate the efficacy of early CCP administration introduces several challenges. These include setting up the clinical trials, identifying and referring patients early in the disease, managing the logistics of CCP transfusion and patients' follow-up, including managing any adverse events. Home transfusion (HT) and out-of-hospital (OOH) are attractive options for early CCP administration and have been practised for standard blood components. However, OOH/HT requires special attention to manage the logistics, complexities and risks of being distant from hospital care. The availability of OOH/HT in different countries and/or the feasibility of establishing an outpatient transfusion programme that could support early CCP administration is unknown.

The International Society of Blood Transfusion (ISBT) initiated a multidisciplinary group to review existing practices on CCP use. A subgroup was formed to review existing practices and trials in early/outpatient CCP use and to assess its potential application via OOH/HT in different countries. This manuscript aims to summarize the current status of early/outpatient CCP use and existing OOH/HT practices.

METHODS

A questionnaire was developed to examine early and outpatient CCP transfusion (Appendix S1). Data were collected from 1 May to 30 September 2021. Participation was voluntary, and consent was obtained by filling in the questionnaire. The questionnaire included two sections; one for participants who have early/outpatient CCP trials in their institutions or countries, and one for participants who do not have such programmes. The first section included 14 questions covering indications for use, patient inclusion and exclusion criteria, timing of CCP administration, follow-up, trial primary and secondary outcomes, product characteristics, administration logistics and funding sources. The second section included details on CCP use during the COVID-19 pandemic and perceived challenges associated with establishing an early/outpatient CCP programme. In addition, six questions addressed the existing practices of OOH/HT transfusion of standard blood components, how transfusion of quarantined individuals due to COVID-19 is facilitated, where transfusions are administered, and what additional precautions are followed. All survey participants were invited to answer questions on existing OOH/HT transfusion programmes in their countries (if present), how they are facilitated, and how patients are monitored for adverse events.

The questionnaire was distributed to members of the ISBT CCP working group and the European Blood Alliance. We also obtained information from the ISBT Board of Directors on practices in countries that were not represented in the working group. Responses received were summarized, and descriptive analysis was performed.

Trials registered on clinicaltrials.gov up to 14 February 2022, were searched by a research team member. The search strategy to identify completed and ongoing studies were performed using the World Health Organization (WHO) COVID-19 Global literature on coronavirus disease Research Database, MEDLINE, Embase, the Cochrane COVID-19 Study Register and the Epistemonikos COVID-19 L*OVE Platform. Data on pre-hospital/early use of CCP were summarized.

RESULTS

A total of 44 country representatives from 32 countries were invited to participate. Forty participants from 31 countries provided information on the existence of early/outpatient CCP and/or OOH/HT transfusion programmes (response rate; 90.9%) (Figure 1). Nineteen participants, representing 17 countries, shared a description of CCP OOH/HT and outpatient transfusion programmes for COVID-19 patients in their institutions (Table S1). This included national blood establishments/blood centres ($n = 6$), regional blood services/blood centres ($n = 2$) and hospital-based transfusion services and blood banks ($n = 11$). Other participants confirmed the lack of OOH/HT transfusion programmes in their institutions and countries.

Early/outpatient CCP use

Early/outpatient CCP trials were conducted in the United States, the Netherlands and Spain. Details of these are described below. In addition, at the time of the write-up, a multicentre trial (Germany, France, the UK) was starting.

A centre in Brazil has a compassionate use programme with the administration of locally collected pathogen-reduced CCP (Intercept, Cerus, USA) with a minimum neutralizing antibody titre of 1:160 for patients >60 years with co-morbidities. CCP (200 ml) is transfused within 5 days of symptom onset, and a positive test for SARS-CoV-2. CCP is administered in an outpatient setting (day-care, emergency room, COVID ward). The primary outcome is death within 28 days, while the secondary outcome is the need for hospitalization. Patients are followed up in person by physicians, and samples are collected for neutralizing antibody testing. The cost of CCP is covered by the patient or his/her health insurance.

Home transfusion

Home transfusion is practised in Australia, the UK, Belgium, France, Japan, Nigeria, the Netherlands, Spain, Italy, Norway, the United States and some provinces in Canada (Figure 1, Table S2). In the UK, HT was

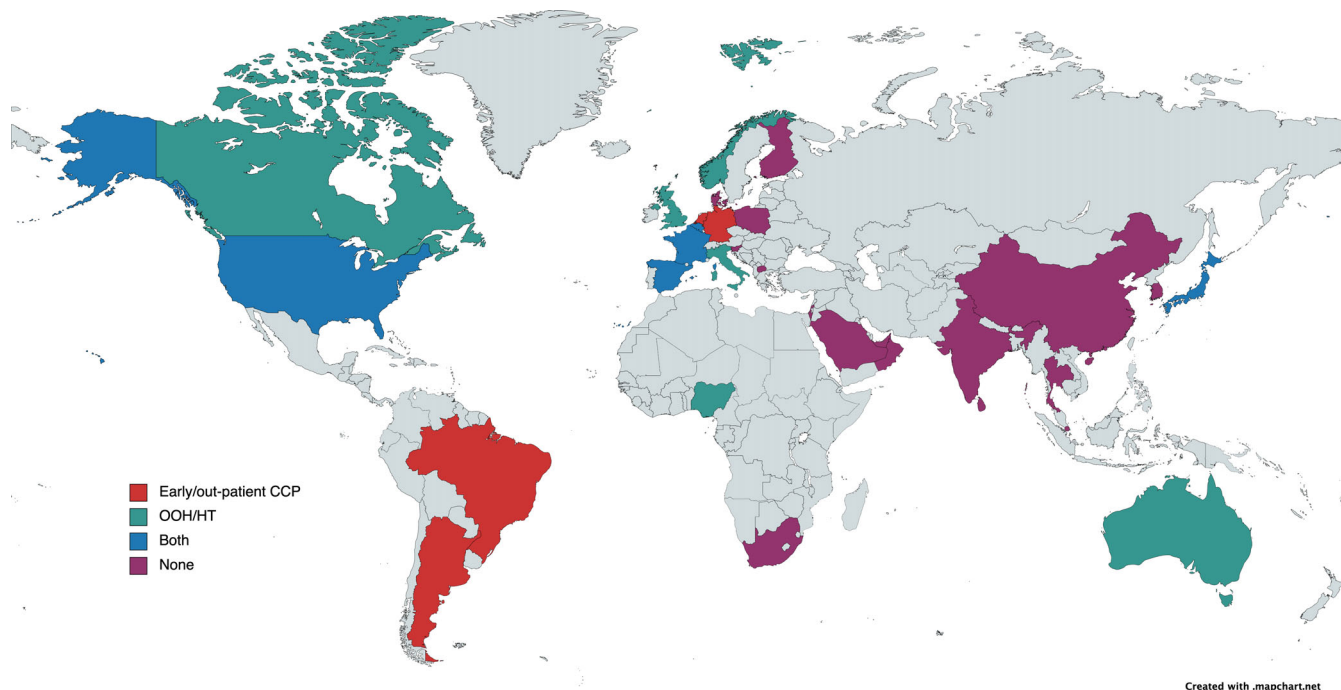


FIGURE 1 Geographic distribution of survey respondents and other participants ($n = 38$)

implemented before the COVID-19 pandemic, but its use has increased substantially during the pandemic. HT is managed by individual hospitals. In France, HT has long been authorized in accordance with existing guidelines. Transfusions are mainly for red blood cells, less commonly for platelets and rarely for plasma. The transfusion is carried out by trained physicians or by medical midwives or nurses, provided that a valid transfusion request is present, and a physician is available to intervene at any time. The practitioner, however, has to be authorized for transfusion in a home-care setting. In Spain, HTs are possible if occurring within 30 min drive from a healthcare facility with ambulance services. Transfusion is performed by a nurse. In Nigeria, several hospitals have home-based care programmes, including HTs that take place under supervision by the clinical team.

The practice of monitoring patients varied between the different countries. In the UK, a nurse needs to be present during the transfusion and for 30 min post-transfusion. Patients are given contact details to report if feeling unwell post-transfusion. A similar practice is followed in Japan. In Spain, the nurse needs to be present for the first 15 min. In France, transfusion is monitored at least for the first 15 min and at regular intervals thereafter, and the healthcare provider must be available for at least 2 h after the end of the transfusion. Family members are instructed to monitor the patient for the first 2 h post-transfusion.

Transfusion of patients with COVID-19

For outpatients with COVID-19 infection, there was variation in the practice of where transfusion of standard blood products was

undertaken should require while being in quarantine outside the hospital (Table S2). This included the emergency room ($n = 9$), COVID wards ($n = 8$), and home ($n = 7$). In a regional blood service/blood centre in the United States, a dedicated outpatient infusion tent is used for this purpose. In Australia and the UK, the transfusion practice varies. In Denmark, Israel, North Macedonia and South Korea, patients are admitted if they require a blood transfusion, while in Belgium, this is arranged through the patient's general practitioner. Standard COVID-19 precautions while transfusing patients were reported to be followed by all participants.

Challenges for establishing an OOH/HT CCP programme

Institutions described different challenges with an OOH/HT CCP programme. These included obtaining institutional review board approval to set up a clinical trial and patient enrolment within a narrow window from symptom onset/diagnosis. Other challenges included the logistics of transfusing CCP outside of a hospital setting and controlling the flow of patients with COVID-19 separately from uninfected patients if transfused in the day-care or emergency room.

Perceived obstacles to starting an OOH/HT CCP programme in countries included the existing regulations/legislation and/or lack of policies pertaining to transfusion outside hospital premises and infrastructure to accommodate a change in practice. Other obstacles included the need for resources (e.g., staffing, funding, equipment for maintaining the cold chain during transfer) and managing the associated logistics. In Thailand, CCP, prepared by the National Blood Centre in Bangkok, is restricted 'for inpatient cases only'.

TABLE 1 Completed studies of COVID-19 convalescent plasma in early/outpatient setting

Study	Country/ies	Intervention(s)	Number analysed	Patient population	Primary outcome(s)	Neutralizing antibody titre	Viral variants considered in analyses
<i>Prophylaxis</i>							
Shoham et al., 2022 (CSCC-001) [13] ^a NCT04323800	USA	200–250 ml CCP 200–250 ml non-immune plasma ^d	180 (Planned 500)	Age ≥18 Close contact exposure to person with COVID-19 within 96 h of randomization (and 120 h of receipt of plasma) Exclusions: ^c <ul style="list-style-type: none"> • Previous COVID-19 • COVID-19 symptoms • Laboratory evidence of COVID-19 at time of screening • Receipt of any blood product ≤120 D 	Cumulative incidence of development of SARS-CoV-2 infection (symptoms compatible with infection and/or + molecular testing) [D28] Cumulative incidence of serious adverse events [D28] Cumulative incidence of grade 3 and 4 adverse events [D28]	≥ 1:320	No Recruited June 2020 to March 2021
<i>Therapeutic (asymptomatic)</i>							
No completed studies							
<i>Therapeutic (mild disease)</i>							
Libster et al., 2021 [6] NCT04479163	Argentina	250 ml CCP 250 ml saline (placebo)	160	Age ≥75 or 65 to 74 and co-morbidity Confirmed SARS-CoV-2 mild illness, not requiring hospitalization ≤72 h from symptom onset	Development of severe disease – defined as RR ≥30 breaths/min or oxygen saturations <93% on air, or both	>1:1000 anti-S IgG SARS-CoV-2	No Recruited June–October 2020
Sullivan et al., 2022 (CSCC-004) ^a [12] NCT04373460	USA	~250 ml CCP ~250 ml non-immune plasma ^d	1181 (Planned 1344 participants)	Age ≥18 (stratified < vs. ≥65 years) Confirmed SARS-CoV-2 not requiring hospitalization ≤8 D from symptom onset Exclusions: ^c <ul style="list-style-type: none"> • Hospitalized or expected to be hospitalized within 24 h of enrolment • Receiving any treatment drug for COVID-19 within previous 14 D • Inability to adhere to protocol • Receipt of monoclonal anti-bodies • Psychiatric or cognitive illness or recreational drug/alcohol use 	Cumulative incidence of hospitalization or death before hospitalization [D28] Cumulative incidence of treatment-related serious adverse events [D28] Cumulative incidence of treatment-related grade 3 or higher adverse events [D90]	≥ 1:320	No Recruited June 2020–October 2021 90% of CCP was donated between April and December 2020
Bart Rijnders et al., 2020 (CoV-Early) ^a [14, 15] NCT04589949	Netherlands	300 ml CCP 300 ml non-immune plasma ^d	420 (Planned 690)	Age ≥70 OR 50–69 AND ≥1 risk factors ^b OR 18–49 and severely immunocompromised RT-PCR-confirmed COVID-19 ≤7 D from symptom onset	Highest disease status [D28]	1/160 Sanquin method, or 1/320 Virosence method	Recruited November 2020–July 2021 for first analysis (Continues)

TABLE 1 (Continued)

Study	Country/ies	Intervention(s)	Number analysed	Patient population	Primary outcome(s)	Neutralizing antibody titre	Viral variants considered in analyses
Alemany et al., 2022 (ConV-ert) [11, 15] NCT04621123	Spain	200–300 ml methylene blue-treated CCP 200–300 ml saline (placebo)	376 (Enrolled 384)	Exclusions: ^c <ul style="list-style-type: none"> Life expectancy <28D Known IgA deficiency or TRALI Admission to hospital Age ≥50 Confirmed SARS-CoV-2 by PCR or antigen rapid test ≤5 D Symptom onset (mild or moderate) ≤7 D Exclusions: ^c <ul style="list-style-type: none"> Pregnant, breastfeeding Severe or critical COVID-19 Current hospital admission History of previous confirmed SARS-CoV-2 infection. Previous COVID-19 vaccination Significant liver dysfunction Chronic kidney disease ≥stage 4, or need of dialysis Increased risk of thrombosis Known IgA deficiency with anti-IgA antibodies Disease in which 200–300 ml fluid volume a risk Inability to adhere to protocol 	Hospitalization rate [D28] SARS-CoV-2 viral load [D7]	EUROIMMUN ratio ≥6	Recruited November 2020 to July 2021 for first analysis
Emergency Room							
Korley et al., 2021 (C3PO) [10] NCT04355767	USA	250 ml CCP 250 ml saline (placebo)	511	Age ≥50 or ≤18 and co-morbidity Confirmed SARS-CoV-2 not requiring hospitalization ≤7 D from symptom onset	Disease progression after randomization [D15] (composite of hospital admission for any reason, emergency or urgent care, or death without hospitalization)	Median neutralizing antibodies 1:640 (IQR 468 to 1702)	No Recruited August 2020–February 2021

Abbreviations: CCP, COVID-19 convalescent plasma; D, days; IQR, interquartile range; RR, respiratory rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TRALI, Transfusion Related Acute Lung Injury.

^aAdditional information provided in survey.

^bObesity, male gender, cardiac, renal, rheumatic or pulmonary disease, and immunodeficiency.

^cHistory of prior reactions to blood transfusion.

^dPlasma collected in 2019, or obtained from persons who tested seronegative for SARS-CoV-2 after Dec. 2019.

Respondents from Bhutan, Nigeria and Japan indicated that there were no CCP programmes in their respective countries.

Another major challenge is the lack of policies and procedures for monitoring and managing adverse reactions post-transfusion in an OOH/home setting. This included defining responsibilities and duration of monitoring patients after transfusion for adverse reactions, and managing these if they occurred, especially if severe. Some indicated the lack of willingness and confidence of the healthcare providers and the caregivers in handling the transfusion.

Published trials

There were six completed randomized control trials on the use of CCP in an outpatient setting or emergency room setting [6, 10–14] (Table 1). Three of the peer-reviewed trials enrolled patients with confirmed SARS-CoV-2 infection to one unit of high-titre CCP versus placebo [6, 10, 11]. Libster et al. [6], treated older patients, mean age 77.2 ± 8.6 years old, very early after symptom onset (within 72 h) who did not need emergency or hospital care. This trial showed the benefit of early administration of high titre CCP in mildly ill, infected older adults with reduced progression to severe disease. Korley et al. (C3PO) [10] and Alemany et al. (ConV-ert) [11] treated younger patients (median 54 and 56 years respectively) within 7 days of symptom onset. Korley et al. sought to determine whether an infusion of high-titre CCP would prevent progression to severe COVID-19 if given to patients at high risk of severe COVID-19 who present to the emergency room (composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization). The ConV-ert study compared standard medical treatment plus methylene-blue treated CCP versus normal saline. No benefit was seen in the primary or secondary outcomes for either trial. In the Korley et al. trial, more participants were admitted to the hospital directly from the emergency department in the CCP arm than in the placebo arm (19 vs. 6). In a post hoc sensitivity analysis that excluded patients admitted to the hospital during their index visit, the posterior probability of superiority of CCP was 93% in the intention-to-treat population. The Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004) trial [12] randomized adult outpatients with COVID-19 within 9 days of symptom onset to receive high-tier CCP versus non-immune plasma, thus demonstrating significantly fewer cases of hospitalization (i.e., the primary endpoint) in those who received CCP as compared to controls (relative risk reduction, 54%). The CSSC-001 [13] compared high-titre CCP versus non-immune plasma as post-exposure prophylaxis. Participants with close contact exposure to someone with confirmed COVID-19 were enrolled; all were negative for SARS-CoV-2 at the time of enrolment. CCP was administered within 120 h of exposure, and patients with symptomatic or asymptomatic COVID-19 infection at the time of screening were excluded. The primary outcome was SARS-CoV-2 infection. The trial was stopped early due to the increased use of vaccination. There was no significant difference seen between the two arms in the number of participants who developed SARS-CoV-2 infection ascertained

by positive reverse transcription polymerase chain reaction (RT-PCR) testing by study day 28. The CoV-Early [14] is a therapeutic trial that enrolled patients aged 50 years or older within a week of symptom onset to receive CCP versus non-immune plasma. CoV-Early was analysed together with ConV-ert on a total of 797 patients within the first 7 days of symptoms using a Bayesian analysis [15]. The results showed no impact on the rate of hospitalization or mortality.

In CSSC-001 and CSSC-004, CCP transfusion was performed in a research unit at hospital sites, and follow-up was undertaken in a specific tent adjacent to the hospital. In the CoV-Early trial, patients were followed up at least by phone to evaluate their disease status and severity on a 5-point scale. Laboratory testing was performed by attendance at the day-care unit/hospital for a subgroup of patients.

Ongoing trials

There are five ongoing/planned trials on early/outpatient and OOH CCP use [16–20]. These trials varied in their source of funding from the government (three; one- USA, one- Germany, one- international); healthcare companies (one; USA); or unclear funding sources (one; Spain) (Table S3). All are therapeutic trials; four use standard-of-care as the comparator, and the fifth (Spain) uses standard plasma. In these therapeutic trials, the time of CCP administration from symptom onset varies and ranges from <96 h to ≤ 14 days. None of the trials included children.

The German trial is a multicentre four-arm trial that compares CCP, camostat mesylate, standard of care, and a placebo to camostat mesylate in a 2:2:1:1 ratio, in symptomatic high-risk patients with confirmed SARS-CoV-2 infection within 3 days of symptom onset and diagnosis [16]. The two ongoing trials from the United States compared CCP with the standard of care, one within 96 h of symptom onset in patients with confirmed SARS-CoV-2 infection plus one high-risk feature, allowing cross-over to the CCP arm should the patient require hospitalization for progression of COVID-19 disease [17]. The other trial enrolls symptomatic patients with mild/moderate laboratory-confirmed disease <14 days from symptom onset [18].

The international trial, which is starting in Germany at the time of writing, aims to assess the effectiveness of CCP (very-high titre plasma [neutralizing Ab titre $\geq 1:640$ against delta variant]) in two different cohorts, (1) older patients (≥ 70 years) or patients with co-morbidities, (2) patients with immunosuppression [19]. The Spanish trial stopped recruitment early due to lack of efficacy of CCP in preventing progression to a severe form of COVID-19 [20]. No trial data are available at the time of writing.

DISCUSSION

Several trials are currently examining the role of early CCP administration in the treatment of COVID-19 on a therapeutic or prophylactic basis. There are six completed therapeutic trials: two showed clinical benefit- one in high-risk participants who were <72 h from symptom

onset [6]; and the largest outpatient trial (1181 participants) showed benefit in people treated within 8 days of symptom onset [12]. The other trials did not show benefit [10, 11, 13, 14]. In C3PO [10], more participants in the CCP arm were admitted to the hospital directly from the emergency department, which meant they met the primary outcome during their initial visit to the emergency department. This could have skewed the findings with potentially more severely unwell participants in the CCP arm. The first randomized clinical trial exploring post-exposure prophylaxis was halted early as it ceased to be feasible given the availability of vaccination [13]. The trial was too small to assess any effect on progression to severe disease or need for hospitalization.

There are several ongoing studies on early administration of CCP, these trials vary with regards to the timing of CCP administration (96 h–14 days), type of comparative arm used (non-immune plasma, saline, standard of care), patient eligibility (healthy adults to elderly or immunocompromised) and primary outcomes analysed (resolution of SARS-CoV-2 symptoms, hospitalization, adverse events or death). Some of these trials did not specify the volume of CCP administered in the treatment arm. The results of these trials will be important in understanding the role of CCP in treating patients early in their disease course.

Early administration of CCP is associated with different logistical challenges, and OOH/HT of CCP offers a suitable option. Data from clinical trials have shown that early CCP administration is not associated with an increased risk of adverse events compared to other blood components [3–5]. Considering the safety profile of CCP, OOH/HT CCP transfusion is an option for patients who are early in their disease course. Our results showed variation in the availability of OOH/HT programmes. Out-of-hospital transfusion has been in practice for many years in different locations, such as patients' homes, hospices and rehabilitation facilities, and in a variety of patients of different ages and diagnoses [21]. Different reports showed that HT is feasible and safe when performed on selected patients by trained staff under specific protocols [22–24]. The main advantage of this practice is facilitating CCP administration early in the disease course, perhaps before the patients develop their own antibodies. Other potential advantages are facilitating patient-centred care, overcoming the challenges of managing the patients in a busy hospital setting, and ensuring complete post-transfusion follow-up for clinical and laboratory monitoring. It can also be an attractive option to enrol patients in clinical trials and reduce the cost of in-hospital care through the provision of such specialized services in their homes. However, setting up such a programme has been associated with different challenges, as described by the participants of this study that may render the feasibility of initiation of OOH/HT programmes difficult during pandemics.

There are essential components of outpatient transfusion programmes that were reported from HT programmes [21, 22] and more recently from CCP transfusion trials [25]. Considering the required staff expertise and resources, OOH/home CCP transfusion should only be offered in facilities with adequate infrastructure and capacity to manage transfusion-associated adverse events [25]. This is particularly important to ensure recipient safety due to the increased risk because of distance from emergency care. The location of the transfusion should be accessible by ambulance, and the distance or time that it would take to travel to a hospital emergency department should be defined [21, 22]. Establishing

temporary facilities, such as annexes from emergency departments or portable treatment facilities, is an option as used in CSSC-001 and CSSC-004 clinical trials [25]. Policies and procedures must be available, and staff training and availability must be considered, with redundancy to cover absences [25]. The enrolment criteria should be specific in enrolling patients who are not acutely ill. Procedures with regard to ABO blood group typing, verification of patient identity and means of access to electronic medical records should be considered [25]. The facility must adhere to all regulations that apply to blood transfusion, including monitoring and reporting transfusion reactions. Instructions should be provided to the patient to report any reactions after the transfusion.

In conclusion, studies are underway on the potential role of early administration of CCP. OOH/HT for early delivery of CCP is attractive in many respects. The results of this international survey identify a number of important practical and logistical challenges that should be addressed in order to ensure the availability of essential resources for an out-of-hospital administration.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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