Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health Technology Assessment Scoping Report

Convalescent plasma for the treatment of COVID-19

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About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
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- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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Abbreviations

EUnetHTA	European Network for Health Technology Assessment
FDA	U.S. Food and Drug Administration
HTA	health technology assessment
IgA	immunoglobulin A
MERS	Middle East Respiratory Syndrome
NRSI	non-randomised study of interventions
PICOS	Population, Intervention, Comparator, Outcomes, and Study type
RCT	randomised controlled trial
RT-PCR	reverse transcription polymerase chain reaction
SARS	Severe Acute Respiratory Syndrome
WHO	World Health Organization

Key findings

The purpose of this scoping report is to provide a preliminary assessment of the current available evidence on convalescent plasma for the treatment of COVID-19, in order to inform consideration by the Minister for Health of its potential use in Ireland.

The Health Information and Quality Authority (HIQA) agreed to undertake this scoping report following a formal request from the Department of Health.

The key findings of this scoping report are:

- To date, there is no effective treatment for COVID-19, or vaccine to protect people against the virus.
- Convalescent plasma from patients recently recovered from a disease contains antibodies which, when transfused into others, may confer passive immunity to the disease in recipients. Passive immunity occurs when someone is given antibodies to a disease rather than producing the antibodies themselves. Convalescent plasma has been proposed as a potential treatment for patients with COVID-19, or as prophylaxis in pre-symptomatic cases at risk of severe COVID-19 disease.
- Although there are limited data on efficacy in patients hospitalised with COVID-19, three randomised controlled trials that ended early reported the same direction of a beneficial effect and were underpowered to determine if that effect was significant. A randomised controlled trial that did complete, found no evidence of effect on a composite outcome of mortality and disease progression.
- Important factors in the successful treatment of COVID-19 with convalescent plasma are likely to include a sufficiently high neutralising antibody titre in the donated plasma and the extent to which the recipient has had a significant antibody response prior to transfusion.
- Safety data have been reported in a range of studies. The rate of potentially transfusion-related severe adverse events appears to be low, although comparative data are limited. The safety data must also be considered in the context of a population of patients mostly with severe or life-threatening COVID-19.
- In the absence of viable treatment alternatives, convalescent plasma may offer a potential therapeutic option for patients at high risk of a severe course

of the disease. If convalescent plasma is introduced as a treatment for COVID-19 in Ireland, the number of eligible patients is likely to be small and hence it may be challenging to design an adequately powered study to evaluate effectiveness.

- Collection of donor plasma requires plasmapheresis facilities, of which there may be limited availability in Ireland. Recruitment of eligible donors could be challenging. The size of the donor pool will be a function of incidence in the months prior to collecting plasma and the proportion of cases sufficiently recovered to donate plasma.

1 Introduction

The purpose of this report is to provide a preliminary assessment of the currently available evidence (including ongoing research) in relation to convalescent plasma for the treatment of coronavirus disease 2019 (COVID-19).

1.1. Background to the request

A request in relation to a potential health technology assessment (HTA) of convalescent plasma for the treatment of COVID-19 was received from the Department of Health.

This scoping report represents an extensive (but not exhaustive) assessment of the available evidence in relation to convalescent plasma for the treatment of COVID-19. While the potential use of convalescent plasma as prophylaxis in individuals at high risk of morbidity and mortality from COVID-19 is briefly mentioned, this topic was not the focus of this report.

1.2. Description

1.2.1. Brief background on COVID-19

In December 2019, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan, China. Since then, the infectious disease has spread rapidly around the world, resulting in a major global public health crisis due to high rates of transmission and substantial morbidity and mortality. On 11 March 2020, the outbreak was declared a pandemic by the World Health Organization (WHO). As of 18 September 2020, more than 30 million cases of COVID-19 have been reported worldwide and over 943,000 deaths have been attributed to the disease.[(1)]

The burden of disease associated with COVID-19 is still uncertain. Early data suggested that the majority of patients with COVID-19 develop mild (40%) or moderate (40%) symptoms, some patients develop severe (15%) acute respiratory illness requiring oxygen support, while others (5%) develop critical symptoms such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury.[(2)] Of the COVID-19 cases diagnosed to date, those with a more severe disease course are likely to be disproportionately represented, as testing in many countries was initially restricted to those with more severe symptoms. Access to testing has now expanded to include those that are paucisymptomatic (i.e., presenting with few symptoms) or with mild disease, as well as asymptomatic individuals in the course of contact tracing or as part of screening or surveillance

programmes. Ongoing evaluation of data will therefore be necessary to accurately determine the burden of COVID-19.

To date, there is no effective treatment for COVID-19, or vaccine to protect people against the virus. The European Medicines Agency (EMA) has provided conditional marketing authorisation for remdesivir for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen.[3] The EMA has also endorsed the use of dexamethasone to treat hospitalised adults and adolescents with COVID-19 who are receiving respiratory support.[3] The US National Institutes of Health stated that there are no FDA-approved drugs for the treatment of COVID-19 (as of 21 September).[4] Due to a lack of definitive clinical trial data, potential treatments are considered as experimental and generally available only through clinical trials or expanded access programmes and restricted to patients with severe or critical disease. For example, in May 2020, the FDA issued an Emergency Use Authorization (EUA) that authorised remdesivir for the treatment of hospitalised patients with severe COVID-19. The FDA has subsequently concluded that the potential benefits of remdesivir outweigh the known and potential risks in the patient cohort.

Outside of standard care for critically ill patients, therapies that have been considered can be broadly grouped under the following headings:[4]

- antiviral therapies (for example, remdesivir, chloroquine or hydroxychloroquine, hydroxychloroquine plus azithromycin, lopinavir/ritonavir and other HIV protease inhibitors)
- immune-based therapies (for example, blood derived products such as convalescent plasma, immunomodulators, such as corticosteroids and interferons, and monoclonal antibodies)
- adjunctive therapies (for example, antithrombitic therapy, vitamin C, vitamin D).

For most of the above therapies, the COVID-19 Treatment Guidelines Panel of the US National Institute of Health (NIH) recommends against their routine use on the basis of insufficient clinical data.

1.2.2. Description of convalescent plasma

Mode of action

Convalescent plasma from patients recently recovered from a disease contains antibodies which, when transfused into others, may confer passive immunity to the disease in recipients. The intervention has historically been used to treat conditions

for which there was no vaccine or pharmacological intervention. It has been shown to be effective in the treatment of diphtheria, pneumococcal pneumonia, hepatitis A and B, mumps, polio, measles and rabies.[5] In the context of COVID-19, convalescent plasma therapy may provide clinical benefit for patients with the disease.

Convalescent plasma therapy has been used during other outbreaks, including severe acute respiratory syndrome (SARS), pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), and Ebola. When compared with standard treatment, previous studies have shown that convalescent plasma therapy in patients with SARS resulted in earlier discharge from hospital, particularly if administered early and resulted in lower viral load in patients with severe influenza.[6-10] However, whether the intervention reduces the risk of mortality is somewhat unclear; previous studies have found inconsistent results with respect to overall mortality.

Although convalescent plasma therapy is generally considered to be safe, there is a risk of adverse events occurring. Some of the symptoms associated with convalescent plasma therapy reported in the literature to date include fever or chills, allergic reactions, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO).[11-13] Rare adverse events associated with plasma transfusions include transfusion-transmitted infections, red blood cell allo-immunisation and haemolytic transfusion reactions.[14] In the context of the COVID-19 pandemic, there is also the potential for additional complications or adverse events due to the increased risk of thromboembolic events in patients with the disease.[15] Klok et al.[16] reported that rates of thrombotic complications may be as high as 31% in critically ill patients with COVID-19. While not reported as an issue to date, the transfer of coagulation factors present in plasma products may therefore be harmful to patients with COVID-19.

While convalescent plasma therapy may provide an effective treatment for COVID-19 in some patients, some of the factors that might impact on its effectiveness include the levels of antibodies present in the plasma and the time at which it is administered in terms of disease progression.

Hyperimmune immunoglobulin prepared from convalescent plasma is a related intervention that has been used in the past. An advantage of hyperimmune immunoglobulin is that it does not contain the potentially harmful coagulation factors present in plasma products. To date, no studies have reported on the use of hyperimmune immunoglobulin to treat COVID-19.[17]

Regulatory status

Neither the European Medicine Agency or the Food and Drug Administration (FDA) in the US, have as yet, approved convalescent plasma therapy for use in COVID-19. However, the European Commission[18] and the FDA have developed guidance on the use of the intervention in patients with COVID-19.[19] Both broadly provide recommendations on the collection, testing, processing, storage, distribution and monitoring of convalescent plasma therapy. The FDA additionally provides recommendations on the pathways for use of investigational COVID-19 convalescent plasma therapy, which include clinical trials, expanded access programmes (for example, in patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomised clinical trials), and single patient emergency IND (Investigational New Drug) requests (for example, by a patient's physician in the event of serious or immediately life-threatening COVID-19 infection).[19]

2 Scope

2.1. Research Question

Table 2.1. Research question outlined in the PICO format

Criteria	Definition
Population	People with laboratory-confirmed COVID-19. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed COVID-19. The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Convalescent plasma therapy
Comparator	Any active treatment, placebo, or standard care.
Outcomes	**Clinical effectiveness** **Primary outcome** ▪ All-cause mortality (survival). **Secondary outcomes** ▪ Length of hospital stay ▪ Viral burden (SARS-CoV-2 RT-PCR negativity) ▪ Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study) ▪ Rates of hospitalisation and of patients entering ICU ▪ Duration of mechanical ventilation ▪ Quality of life. **Safety – Main outcomes** ▪ Adverse events (AE) ▪ Severe adverse events (SAE) ▪ Withdrawals due to AEs ▪ Most frequent AEs ▪ Most frequent SAEs.
Study design	Eligible studies will be assessed for suitability with reference to the hierarchy of evidence.

3 Literature search

Through our involvement in the EUnetHTA collaboration, we were aware of the scheduled completion of a rolling collaborative review addressing the research question of interest here.[20] That review includes a description of the technology and addresses the safety and efficacy of convalescent plasma. The evidence contained in that report was supplemented by a search of the literature conducted on 18 August 2020, followed by a further search on 21 September 2020. The search used the *PubMed Clinical Queries Tool* in line with HIQA's standard operating procedure for the conduct of scoping reports. The following search terms were used: (convalescent plasma) AND (COVID-19 OR coronavirus OR SARS-CoV-2). Results were limited to English language studies conducted in humans and published since the start of 2020. Titles and abstracts were reviewed for relevance by one reviewer.

The search was supplemented by ad hoc internet searches, in addition to targeted searches of the websites of HTA agencies and public health bodies.

4 Potential clinical impact

Data on clinical impact was derived from a combination of randomised controlled trials (RCTs), non-randomised studies of interventions (NRSIs) and observational studies. From the literature search, six review articles were identified.[7, 20-24] Two of the reviews were not restricted to COVID-19, and included studies of acute infection with coronavirus, influenza and Ebola virus.[7, 24] Between those two early reviews, only one study of COVID-19 was identified. With the rapidly emerging evidence base, subsequent reviews have been able to identify additional COVID-19-specific studies. The findings presented here include the evidence presented across all of the identified reviews.

4.2. Efficacy outcomes

Efficacy data were available from four RCTs, one from China,[25] two available only as preprints from the Netherlands[26] and Spain,[27] and a fourth from India.[28] With the exception of the Indian study, the other three trials were terminated early.

Li et al. report an RCT from China including 103 patients (52 randomised to standard treatment, 51 to standard treatment plus convalescent plasma) with severe and life-threatening COVID-19 infection.[25] Of the participants, 73% required supplemental oxygen and or non-invasive ventilation, and 25% required extracorporeal membrane oxygenation (ECMO) and or invasive mechanical ventilation. The other 2% of participants did not require supplemental oxygen. The trial was terminated early when no new cases were reported for seven consecutive days; the planned sample was 200 patients. The median age of patients was 70 years. Across all patients, there was no statistically significant difference in clinical outcomes (time to clinical improvement, clinical improvement rate, discharge rate, time to discharge and mortality). However, a subgroup analysis of those with severe disease found a statistically significant improvement in that subgroup in time to clinical improvement (4.9 days, 95% CI: 0.5 to 9.3 days) and clinical improvement rate at 14 days (34%, 95% CI: 6% to 61%).

Gharbharan et al. report on an RCT from the Netherlands with 86 patients (43 randomised to standard treatment, 43 to standard treatment plus convalescent plasma).[26] Of the study participants, 75% required supplemental oxygen and or non-invasive ventilation, and 15% required extracorporeal membrane oxygenation (ECMO) and or invasive mechanical ventilation. The remaining 9% of participants did not require supplemental oxygen. The trial was terminated early when it became clear that some included patients had high virus neutralising antibody titres at study enrolment while some donors had low antibody titres, reducing validity of the results given that the study population could not all benefit from the intervention. The

authors therefore questioned the validity of their results on the grounds that the study population could not all benefit from the intervention. Of the enrolled patients, there was no statistically significant difference in mortality, improvement in disease severity or time to discharge. The authors determined that the adopted patient and donor recruitment strategies were inadequate and would need to be revised for future studies.

Avendaño-Solà et al. report on a Spanish RCT which terminated after 81 patients had been randomised, (43 to standard treatment, 38 to standard treatment plus convalescent plasma).[27] Of the study participants, 72% required supplemental oxygen and or non-invasive ventilation and 28% of participants did not require supplemental oxygen. None of the participants required extracorporeal membrane oxygenation (ECMO) and or invasive mechanical ventilation. The trial was stopped after the first planned interim analysis primarily due to a fall in recruitment. The primary endpoint was worsening (on an ordinal scale) at 15 days, with progression observed in none of the intervention arm patients and six control arm patients. Although not statistically significant in the planned statistical analysis, it was shown to be statistically significant in a post-hoc sensitivity analysis. While patients in the convalescent arm had lower rates of worsening symptoms at 15 and 29 days, lower mortality and time to improvement, these were not statistically significant.

Agarwal et al. report an RCT from India with 464 patients (229 randomised to standard treatment, 235 to standard treatment plus convalescent plasma; intention to treat analysis) with severe COVID-19 infection.[28] Of the included participants, 78% did not require supplemental oxygen, and 22% required supplemental oxygen and or non-invasive ventilation. One participant required oxygen by non-invasive ventilation of high flow. The median age of patients was 52 years. Across all patients, there was no statistically significant difference in a composite outcome of mortality at 28 days and progression to severe disease. However, treatment with convalescent plasma was associated with higher resolution of shortness of breath and fatigue on day seven. Patients and donors were not selected based on antibody titres at enrolment.

Based on the efficacy data of the RCT by Li et al., the outcomes are considered as having a low certainty of evidence.[20, 21] While the subgroup with severe, but not life-threatening COVID-19 may stand to gain, the evidence is based on only 45 patients in a trial that was terminated early and powered only for a difference across all patients. In both the Dutch and Spanish RCTs the direction of effect for convalescent plasma is beneficial, but neither demonstrated a statistically significant effect. It is important to bear in mind that the included studies did not select participants (patients or donors) for neutralising antibody titres. As such, some patients had high neutralising antibody titres at the outset, and some donors had

low titres. It is unclear if a patient with a high neutralising antibody titre would stand to gain from being transfused with plasma with a low neutralising antibody titre.

4.2. Effectiveness outcomes

The Cochrane review included three controlled non-randomised studies of interventions that reported clinical outcomes.[21] All were judged to be at critical risk of bias across a number of domains. The included studies predominantly involved patients that were described as severely or critically ill. The following paragraphs summarise the key findings from the Cochrane review in relation to effectiveness outcomes.

In terms of time to death, a single study reported prolonged time to death with convalescent plasma (very low certainty of evidence).

Three studies reported on improvement in clinical symptoms, but due to differences in outcomes measures and follow up, the data could not be combined. One study reported on the reduced need for respiratory support at day 14 (odds ratio 0.86, 95% CI: 0.75 to 0.98). Another study reported hospital discharge at unspecified last follow up (odds ratio 2.80, 95% CI: 0.15 to 53.7), with only one surviving patient in both the intervention and control groups. A third study only reported improvement in clinical symptoms in the intervention group.

Three studies reported on the proportion of patients discharged at the longest available follow up. None of the three studies found a statistically significant difference between the intervention and control groups.

A US study was identified that had not been included in the Cochrane review. The study used propensity score matching to retrospectively identify controls for 39 convalescent plasma recipients.[29] Analyses were performed with controls matched in 1:4 and 1:2 ratios across a range of characteristics. The authors found that oxygen requirements and mortality were lower in the convalescent plasma group. However, the non-randomised nature of the study design means that there may be important systematic differences between cases and controls. For example, the cases were more likely to have received anticoagulant compared to their matched controls.

4.3. Safety outcomes

Safety data were reported in the RCTs providing efficacy data. In the RCT from China, two patients in the convalescent plasma arm developed adverse reactions, one non-severe and one severe, and both recovered.[25] In the RCT from the Netherlands, no plasma related serious adverse events were observed.[26] The

Spanish trial reported two intervention-related adverse events; both patients recovered without sequelae.[27] The Indian RCT reported a number of adverse events including pain at the infusion site, chills, nausea, bradycardia, dizziness, fever and tachycardia.[28] The latter trial reported three deaths (1%) possibly related to convalescent plasma transfusion.

The Cochrane review included safety data from 14 controlled and non-controlled NRSIs.[21] The EUnetHTA review[20] contained data from five prospective observational studies, two of which had been included in the Cochrane review. None of the three additional studies reported serious adverse events. A review of efficacy and safety identified five studies with safety data, one of which was a short case-series not included in the Cochrane review.[22] Finally, the systematic review of Sarkar et al. identified an additional retrospective study, but safety outcomes were not reported.[23] With the exception of one case series of five patients, all studies reporting safety outcomes are contained in the Cochrane review, and this section will focus on the results reported in that review.

For safety outcomes, the focus is on patients who received convalescent plasma. Of the 14 studies with safety data included in the Cochrane review, one US study included 5,000 patients while the other 13 studies included a combined total of 201 patients. Most studies reported the occurrence of adverse events, but provided limited or no detail on the nature of the events or degree of severity.

In four studies, adverse events were reported that could potentially be grade 3 (severe and undesirable) or grade 4 (life threatening or disabling):

- Li et al. (2 of 52 participants)
- Perotti et al. (4 of 46 participants)
- Tan et al. (a case study)
- Pei et al. (1 of 3 participants)

Four studies reported serious adverse events:

- Joyner et al. (four of 5,000 died potentially/probably/definitely because of transfusion; 11 of 5,000 had transfusion-related acute lung injury; seven transfusion-associated circulatory overload; three severe allergic reactions)
- Li et al. (1 of 52 participants)
- Perotti et al. (3 of 46 participants)
- Pei et al. (1 of 3 participants).

The Cochrane review noted that duration of follow up varied across studies and it was not always clear from studies whether the adverse events were related to transfusion. The US study is by far the largest study and does report where the adverse events are transfusion-related. However, the US study limits observation to

the first four hours after convalescent plasma transfusion, and may therefore underestimate adverse events. The Cochrane review graded the level of evidence on serious adverse events as being very uncertain.

The large US study was reported as an analysis of a convenience sample of 5,000 patients in an ongoing US FDA Expanded Access Programme. The study includes hospitalised adults that had (or were judged to have high risk of progression to) severe or life-threatening COVID-19. Since the Cochrane review was published, the authors have published a follow up that reports on 20,000 patients.[30] The follow up includes serious adverse events that were reported up to seven days after transfusion. A total of 146 serious adverse events were reported, including:

- 13 (0.07%) died potentially/probably/definitely because of transfusion
- 20 (0.10%) had transfusion-related acute lung injury
- 37 (0.19%) transfusion-associated circulatory overload
- 26 (0.13%) severe allergic reactions.

For context, while 13 deaths were associated with convalescent plasma transfusion, a total of 1,711 deaths were reported emphasising the high seven day mortality rate in the patient group. The study reports on an ongoing programme and it is likely there will be further reports published in due course.

4.4. Ongoing studies

There are a large number of planned and ongoing studies of convalescent plasma for the treatment of COVID-19. A recent survey identified 64 clinical trials, including RCTs and case series.[31] Few of the studies plan to have more than 200 patients in the intervention arm, and almost all focus on hospitalised or critically ill patients. It is unclear whether trials include eligibility criteria in relation to the antibody response of patients at the time of study enrolment.

A number of case-series have been published that focus on specific patient subgroups that may be at high risk of severe COVID-19 disease. Examples of identified subgroups include: solid organ transplant recipients,[32] cancer patients,[33] and those with sickle cell disease.[34] In these cases, convalescent plasma has been administered as a treatment for patients with COVID-19. For individuals with certain underlying conditions, there may also be the prospect of post-exposure prophylaxis to prevent infection.[35]

5 Potential organisational impact

The provision of convalescent plasma as a treatment for patients with COVID-19 will have a number of organisational implications. The eligibility and suitability of patients must be considered, as must the identification and recruitment of suitable donors.

5.1 Inclusion/exclusion criteria for plasma recipients

Not all patients with COVID-19 will be eligible or suitable for convalescent plasma therapy. Three of the RCTs identified in the literature search, for example, restricted treatment to hospitalised patients with approximately three quarters of participants requiring supplemental oxygen and or non-invasive ventilation.[25-27] The exception was the Indian study where three quarters of participants did not require supplemental oxygen.[28] In evaluating the evidence of efficacy, it is important to consider the inclusion and exclusion criteria for trial participants.

For the three RCTs, the main inclusion criteria included:

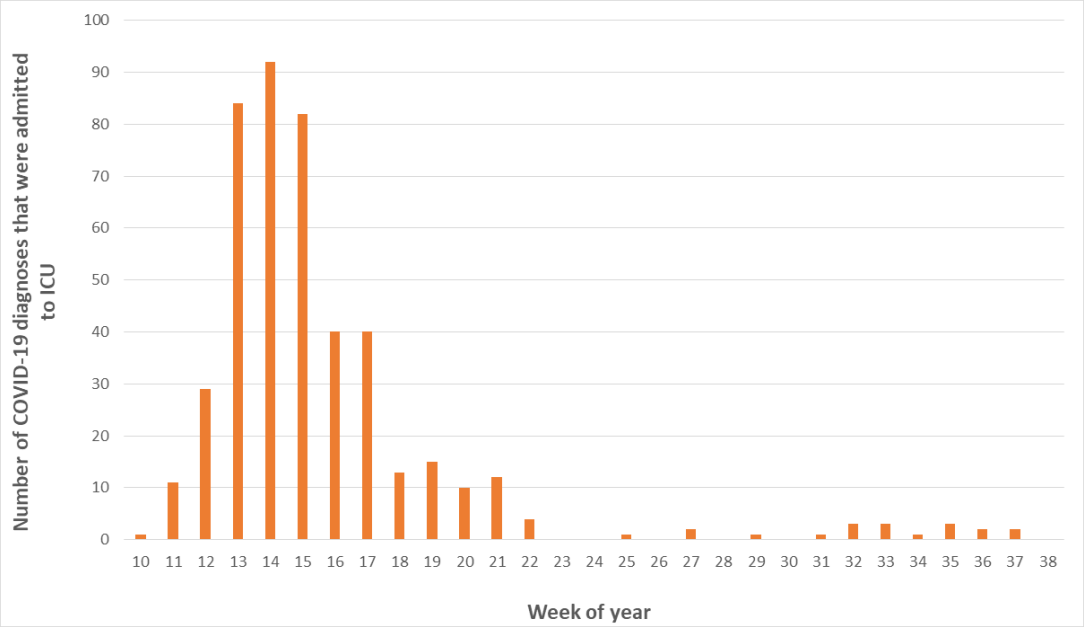
- aged at least 18 years
- COVID-19 diagnosis based on polymerase chain reaction (PCR) testing
- positive PCR result
- pneumonia confirmed by chest imaging or clinical assessment
- clinical symptoms meeting the definitions of severe or life-threatening COVID-19
- hospital admission.

The exclusion criteria included the following:

- IgA deficiency
- mechanical ventilation for >96 hours (any mechanical ventilation in the Spanish RCT)
- pre-existing comorbidity that could increase the risk of thrombosis
- life expectancy less than 24 hours
- pregnancy or lactation
- immunoglobulin allergy
- disseminated intravascular coagulation
- severe septic shock
- Pao2/Fio2 of less than 100
- severe congestive heart failure
- stage 4 chronic kidney disease or requiring dialysis
- detection of high titre of S protein–RBD-specific (receptor binding domain) IgG antibody (≥1:640).

It is unclear how many patients in Ireland would be considered eligible for convalescent plasma and for whom it would be considered. Irish data regarding the number of cases that are admitted to ICU may represent an indicative figure for those with severe or life-threatening disease (Figure 5.1). Discounting the most recent week of data (on the grounds that cases diagnosed in the most recent week may not yet be hospitalised or admitted to ICU), the average number of cases requiring ICU admission over the previous six weeks (weeks 32 to 37) was 2.3 per week.

Figure 5.1 Numbers of COVID-19 diagnoses per week of year (that at some point were admitted to ICU)



Depending on the eligibility criteria for recipients of convalescent plasma, cases requiring ICU admission may be a poor measure of potential demand. For example, if convalescent plasma was considered for individuals at high risk of complications or severe disease, that is, those at risk of ICU admission, then demand may be much higher. The extent to which demand is higher than ICU attendance will depend on the accuracy of the available prognostic instruments; accurate prognosis will minimise demand to those at highest risk of severe disease.

5.2 Dosage

The reported dosage varies across studies, but was typically equivalent to one unit followed by a second in patients without a clinical response and a persistently positive RT-PCR. One patient will therefore require between one and two units, although the volume of one unit was not uniform across studies. The RCT published by Li et al. indicated that 96% of recipients required only a single unit.[25]

- In the Chinese RCT, the transfusion dose of COVID-19 convalescent plasma was approximately 4 to 13ml/kg of recipient body weight.[25] Convalescent plasma transfusion was administered at approximately 10ml for the first 15 minutes, and then increased to approximately 100ml per hour with close monitoring. At the discretion of the treating physicians, adjustments in the infusion rates were allowed based on the patient's risk for volume overload and tolerance.

- In the Dutch RCT, the standard of one 300ml plasma unit produced by Sanquin Blood Supply was administered intravenously on the day of inclusion. Patients without a clinical response and a persistently positive RT-PCR could receive a second plasma unit after five days.[26]

- In the Spanish RCT, patients received a single dose (250 to 300ml) of convalescent plasma which was administered immediately after randomisation.[27]

- In the Indian RCT, patients were scheduled to receive two doses of 200ml of convalescent plasma, transfused 24 hours apart.[28] The first dose of convalescent plasma was transfused at randomisation. The two plasma units were collected preferably from different donors.

It was highlighted in the trials that the ABO type of the convalescent plasma transfused had to be compatible with the patient's ABO type. In Li et al., the convalescent plasma was also cross-matched with the patient's red blood cells to ensure compatibility.[25]

5.3 Donors

The provision of convalescent plasma is contingent on the recruitment of suitable donors. Typical inclusion criteria for plasma donors are age (18 to 55 or 18 to 60 years), at least 14 days since clearance of COVID-19 infection as measured by two successive negative PCR test results, and standard donor eligibility criteria.[36] Under the current FDA recommendations, female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for human leukocyte antigens antibodies are eligible.[36] In Italy, eligibility also included a negative history of blood component transfusion.[37]

Plasmapheresis should be undertaken at certified blood establishments. The volume collected should be at least 200 to 600ml (without anticoagulant).[38] The frequency of donation for an individual donor must be compliant with standard practice in Ireland. Plasma units should be clearly labelled as being for the purpose of convalescent plasma for COVID-19.[37, 38]

In a study of 126 plasma donors, Klein et al.[39] found that male donors and hospitalisation for COVID-19 are predictors of overall greater antibody titres. The difference by sex was less pronounced than the difference by hospitalisation. The antibody titre is often characterised by the viral neutralisation titre, although it has not been proven how it relates to in vivo potency and hence may be a poor predictor of potential efficacy.[40]

Based on an analysis of 49 donors, Li et al.[41] suggested a number of criteria for selecting plasma donors: 28 days after the onset of symptoms and with a disease presentation of fever lasting longer than three days or a body temperature exceeding 38.5°C. Cases were identified through hospital records (i.e., they had been hospitalised with COVID-19).

The antibody response changes over time in those who have recovered from COVID-19 infection. Li et al. suggest that donation should occur at least 28 days since symptom onset, and two weeks since the clearance of COVID-19 infection.[41] Waning immunity could mean that there may be a preference for recently recovered patients over those that may have been infected four or five months before donation. If there is a prolonged period of low incidence then there could be major challenges in recruiting donors, particularly for rare blood types.

A recently published multi-centre study reported an association between neutralizing antibodies to type I interferons and severe COVID-19 pneumonia.[42] It concluded that patients with neutralizing antibodies against type I interferons recovering from life-threatening COVID-19 pneumonia should be excluded from donating convalescent plasma or, at a minimum, be tested before their plasma is accepted.

A US study identified a number of essential elements for a convalescent plasma programme:[43]

- Available donors who have recovered from the disease and meet eligibility criteria to donate convalescent serum; special attention will be necessary to assure that plasma donation will be safe for the recovering patient/donor.
- Develop an approach to screening recovered COVID-19 patients to identify potential donors. Recovery will need to be demonstrated with antibody screening and with appropriate standardised viral nucleic acid testing (for example, RT-PCR), which is important because severe cases have tested positive for SARS-CoV-2 at or beyond day 10 post-symptom onset.[44]
- Recently approved serological assays are necessary to detect SARS-CoV-2 in serum and virologic assays to measure viral neutralisation, which requires

infrastructure and personnel to perform antibody titres in eligible donors, and an understanding of the type of antibody being measured.

- Select desired antibody level in donors, preferably with high neutralising antibody titres (FDA has recommended a titre of>1:320 for eIND).
- Identify blood banking facilities to process the plasma donations (experience with plasmapheresis).
- Select specific product to be prepared (for example, FFP, fresh plasma, or lyophilised plasma), determine and standardise the amount of plasma to be collected and product volume.
- Establish a dosage schedule based on knowledge of SARS-CoV-2 antibodies.
- Consider establishing a registry for possible future donations.

Donated plasma should be subject to a range of treatments including:[38]

- Where feasible, pathogen inactivation of plasma using a licensed technology is highly desirable to control residual risks of transfusion-transmitted infectious diseases and to ease concerns about possible superinfections with SARS-CoV-2.
- Freezing as soon as possible at -20°C, or preferably colder, and stored frozen until administration.
- Convalescent plasma collected from donors who do not fulfil post-COVID-19 suitability criteria for blood donation should be stored separately from other blood products in inventory.
- Plasma sample aliquots should be taken for archiving at -80°C and future potential scientific investigations.

In the event that convalescent plasma is made available as a treatment option, consideration has to be given to how potential donors might be identified and contacted. Hospitals may offer the most efficient route to donor identification, because of their ability to identify and test COVID-19 positive patients.[36] Prospective identification and recruitment of potential donors at hospital discharge may be more efficient than recall of patients post-discharge, assuming that the donor pool will primarily comprise patients with sufficient illness severity to be hospitalised. Targeted recruitment will have to be considered to maximise the prospect of an adequate supply of plasma.[45] The approach to potential donor

identification must comply with General Data Protection Regulation (GDPR) legislation.

The inclusion/exclusion criteria combined with logistical issues relating to where plasmapheresis can be carried out may have implications for the size of the donor pool. If there are limited sites that can carry out plasmapheresis, then the donor pool may be limited to those who can readily travel to those sites. Estimating the potential donor pool is challenging, although it is possible to generate an approximate upper bound estimate. HSE data indicated that based on hospitalised cases from the last three months (to 21 September 2020), aged 18 and 64 years and not known to have died, there are limited potential donors (Table 5.1). Clearly some of those presumed to be eligible donors may not in fact be eligible due to the exclusion criteria that apply to those donating blood products in Ireland. It should also be borne in mind that not all potentially eligible donors will have sufficiently high neutralising antibody titres. Equally, some potentially eligible donors may maintain high titres of neutralising antibodies for longer than three months, so that the potential donor pool could be extended to those hospitalised with COVID-19 several months earlier.

Table 5.1 Potential donor pool by region

Region	Females	Males
Connaught	<5	<5
Dublin	21	16
Leinster	8	5
Munster	5	11
Ulster	<5	5

Based on HSE data of those aged 18-64 years hospitalised with COVID-19 between 21/06-21/09/2020

The numbers of potential donors reflects the fact that Ireland experienced a period of relatively low incidence during June, July and August. If there is a period of increased incidence, then the potential donor pool will increase accordingly. It should also be noted that a single individual can donate weekly so that one donor could provide plasma to treat multiple patients.

The duration for which plasma can be stored prior to use depends on the storage temperature and processing. At -30°C, plasma can be stored approximately two years, while at -65°C it can be stored for up to seven years.

In the event that convalescent plasma is introduced as a treatment for COVID-19 in Ireland, consideration would have to be given to ensuring equitable access to treatment across hospitals.

No studies were identified that considered the cost-effectiveness of convalescent plasma for the treatment of COVID-19.

6 Decision-making and or policy considerations

There are limited treatment options for those with severe or life-threatening COVID-19. The pharmacological treatments under consideration are supported by limited evidence.

The evidence base on the efficacy of convalescent plasma for COVID-19 comes from four RCTs, three of which had small sample sizes and terminated early. On the basis of those four trials, convalescent plasma is not more efficacious than standard care, although it may be for those who have serious, but not life-threatening COVID-19. Therefore, at present, there is limited evidence on effectiveness, it is at high risk of bias, and the evidence is restricted to hospitalised patients with severe or life-threatening COVID-19. It is plausible that effectiveness may be greater in patients at risk of, but prior to, developing severe or life-threatening disease. There are a number of ongoing RCTs due to complete in the latter part of 2020. As they are completed and published, the extent to which convalescent plasma is effective and which patients may be most likely to benefit may become clearer.

The effectiveness of convalescent plasma is likely to be a function of the neutralising antibody titre of the donated plasma and the antibody response in the recipient at the time of transfusion. The timing of the intervention may also be important. Targeted selection of donors and recipients may improve effectiveness. Studies published to date have focused on convalescent plasma as a treatment in patients with active COVID-19 infection. Future studies may also investigate prophylactic post-exposure use of convalescent plasma in patients at high risk of severe COVID-19, although none had been identified as part of an international survey of trials.[31]

A number of studies which reported safety data have been published. The largest of these, from the US, includes 20,000 patients, but has no control arm. The rate of serious adverse events is low, but in the absence of a control arm and effectiveness data, it is not possible to assess the balance between the benefits and the risk of harm.

In the event that convalescent plasma is introduced as a treatment for COVID-19 in Ireland, the number of eligible patients is likely to be small. It will therefore be challenging to design an adequately powered study to evaluate effectiveness locally. While there may be prospects to harness data from across countries, differences in trial design, patient characteristics and outcomes could limit the ability to appropriately analyse the data.

A position paper developed by the WHO Blood Regulators Network concluded that convalescent plasma or serum should be considered as a candidate intervention in

the setting of an expanding viral epidemic, for which antiviral drugs and vaccines are unavailable.[46] Convalescent plasma might therefore be considered important for national epidemic preparedness, and should be underpinned by an infrastructure for its safe collection and use. If convalescent plasma is to be used as a treatment in the absence of high quality trial evidence, then it will be critical that a structure is put in place to monitor its usage and the clinical outcomes of recipients.

7 Conclusions

Although there are limited data on efficacy in patients hospitalised with COVID-19, three trials reported the same direction of a beneficial effect and were underpowered to determine if that effect was significant. One trial that completed planned patient enrolment found no evidence of effect in the primary outcome. There are a number of ongoing RCTs due to be completed in the latter part of 2020. As they are completed and published, the extent to which convalescent plasma is effective and which patients may be most likely to benefit may become clearer. Safety data have been reported for a large cohort of convalescent plasma recipients in the US. While comparative data are not available, the rate of potentially transfusion-related severe adverse events appears to be low. The safety data must also be considered in the context of a population of patients mostly with severe or life-threatening COVID-19.

In the absence of viable treatment alternatives, convalescent plasma may offer a potential therapeutic option for patients at high risk of a severe course of disease. If convalescent plasma is introduced as a treatment for COVID-19 in Ireland, the number of eligible patients is likely to be very small and hence it will be challenging to collect meaningful data on effectiveness. Collection of donor plasma requires plasmapheresis facilities, of which there may be limited availability in Ireland. Recruitment of eligible donors could be challenging as the donor pool is likely to be small due to the exclusion criteria.

The scoping report was limited to an assessment of the use of convalescent plasma as a potential treatment for patients with COVID-19 experiencing, or who are at risk of experiencing a severe course of disease. The role of convalescent plasma as a component of national strategic pandemic planning, including its potential use as prophylaxis in individuals exposed to COVID-19 who are at high risk of morbidity and mortality, were not the focus of this report.

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