

Recommendations for Convalescent Plasma (CP) use during a pandemic

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Record of Changes

	Authors	Date	Description
1.	David J Roberts, Lise J Estcourt, Abigail A Lamikanra	June 15 th , 2023	First Draft
1.1	David J Roberts, Lise J Estcourt, Abigail A Lamikanra	June 26 th , 2023	First Draft reviewed
1.2	David J Roberts, Lise J Estcourt, Abigail A Lamikanra	June 28 th , 2023	Second review
2.0	David J Roberts, Lise J Estcourt, Abigail A Lamikanra with comments by Dragoslav Domanovic and WP leaders	June 29 th , 2023	Draft for 30 th June
3.0	David J Roberts, Lise J Estcourt, Abigail A Lamikanra with comments by Pierre Tiberghien, Dragoslav Domanovic and WP leaders	July 3rd, 2023	Draft with further EBA comments
4.0	David J Roberts, Lise J Estcourt, Abigail A Lamikanra with comments by Pierre Tiberghien, Dragoslav Domanovic and WP leaders	July 5th, 2023	Draft for circulation to the EBA
5.0	David J Roberts, Lise J Estcourt, Abigail A Lamikanra with comments by Pierre Tiberghien , Dragoslav Domanovic and WP leaders	July 25th, 2023	Draft for final review
6.0	David J Roberts, Lise J Estcourt, Abigail A Lamikanra with comments by Pierre Tiberghien , Dragoslav Domanovic and WP leaders	August 11th 2023	Interim Draft
7.0	David J Roberts, Lise J Estcourt, Abigail A Lamikanra with comments by Pierre Tiberghien , Dragoslav Domanovic and WP leaders	December 19th 2024	Final Draft

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The Pandemic and the Funding Response

The end date of the SUPPORT-E project was given a no-cost extension for two and a half years to 31st December 2024. This is an update to the initial version of this report in August 2023. The data and results given here now provide the recommendations for funding the use of convalescent plasma (CP) to enable preparedness for future pandemics of infectious disease. In the last 18 months, we have:

- collected additional data on completed clinical trials
- supported a selected study of COVID-19 convalescent plasma (CCP) efficacy (or use) in immunocompromised patients positive for COVID-19 before they require admission to hospital (COVIC-19 trial)
- updated the health economic analysis with appropriate models and described the health and economic benefits of collecting plasma
- developed six recommendations described within Section 5.6 of this document.

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Task 5.1 Integrate all project-generated information.

Task leaders: NHBST jointly with EFS.

What has been done between August 2023 to December 2024

Further to the fifth update of the systematic review (Iannizzi, et al., 2023b) that summarised data from patients enrolled in trials conducted globally, we have completed a sixth update, up to 18th October 2024 (Iannizzi, et al., in preparation).

Transfusion of CCP to prevent COVID-19 infection.

Given the low certainty of evidence (Appendix 1) we would recommend against prophylactic transfusion of CCP of individuals who have had close contact exposure to a person with COVID-19 but are not yet infected.

Transfusion of CCP in addition to the usual standard of care to outpatients with COVID-19 at high risk of disease progression

For this most recent analysis, there were two new studies to add to the five in the fifth update. Completion of the COVID-19 randomised controlled trial (RCT) (WP2), which administers high-titre CCP to vulnerable individuals within 7 days of symptom onset, has added valuable evidence for recommended use of CCP in this cohort. CCP may be beneficial to vulnerable individuals (Appendix 3).

To improve our preparedness for pandemics of other infectious diseases, clinical trials should investigate, early within the first months of the pandemic, whether (CP) transfusion is effective in addition to the usual standard of care to infected outpatients who are at high risk of disease progression. As soon as the ability to assess the antibody potency of plasma is made available, only CP with a high titre of antibodies should be used (Libster et al, 2021; Körper et al, 2021).

Transfusion of CCP to treat hospitalised (inpatients) with moderate or severe COVID-19

Here, inpatients are defined as all patients who have been hospitalised or admitted to intensive care with confirmed SARS-CoV-2 infection.

A high certainty of evidence was available from 37 trials to strongly recommend against using CCP transfusion in addition to the usual standard of care for immunocompetent inpatients with COVID-19. The results show that, overall, CCP is not beneficial for hospitalised patients with moderate or severe COVID-19 (Appendix 5). However, these findings are based on RCTs that investigated the use of CCP with variable antibody titres and the outcomes may have been different overall when CCP with a very high titre was used (Körper et al, 2021) and given earlier in severe disease (Misset et al, 2023). Again, data from RCTs are insufficient to make a recommendation for immunosuppressed patients (Appendix 5) and we await the results from the REMAP-CAP RCT that is comparing

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transfusion of very high-titre CCP from vaccinated CCP donors to Standard of Care (SoC) in hospitalized immunosuppressed COVID-19 patients. Our recent update of the systematic review that included RCTs (Appendix 5), strongly suggests transfusion of immunocompromised patients with CCP is beneficial especially when there are no alternatives, although further evidence is needed for definitive international recommendations. In a future pandemic, clinical trials should address the efficacy of CP in immunosuppressed patients (and other vulnerable clinical groups) through the use of RCTs as a matter of priority.

Transfusion-related events

Overall, it was uncertain whether CCP increases or reduces the risk of transfusion adverse events because most studies did not provide full reports of such events for control groups (Appendix 9 reports serious adverse events). Although distinguishing the symptoms of severe COVID-19 disease from known adverse events due to transfusion may be subjective; data for outpatients (with mild disease) are incomplete (Appendix 9A).

What needs to be done

The review suggests that CCP may be efficacious for the treatment of immunocompromised patients who are hospitalised with COVID-19, although further evidence is needed for definitive international recommendations.

One trial aims to gather definitive high-quality evidence of the benefit of CCP in immunocompromised inpatients. The immunoglobulin domain of the REMAP-CAP trial has restarted to recruit immunocompromised patients hospitalised with moderate or severe disease from COVID-19. It has currently recruited 56 participants.

This trial is examining the use of very high-titre CCP collected from vaccinated donors because it has very high concentrations of neutralising antibodies (nAbs) with broad spectra of activity to neutralise not only the early variants of SARS-CoV-2 but up to and including the latest circulating variants. This trial aims to strengthen the evidence for the appropriate and effective use of CCP for the pre-specified immunocompromised sub-group that experiences moderate or severe disease.

Task 5.2 Health Economics

Task leader: NHSBT; Contributing partners: All partners (Task leader NHSBT responsible)

What has been done

The Health Economics Research Centre (HERC), University of Oxford has developed a mathematical model to assist with understanding the financial resources required to establish a CP collection programme in response to a pandemic. This model and analyses assess the affordability of such a programme and provide information for national-level decision-makers for planning purposes. The original aim was to use budget impact analysis of CCP programmes, in which the likely change in expenditure resulting from implementing CP nationally over a period of 1 to 5 years would be estimated for countries across Europe. However, given the uncertainty of how CCP will be used, HERC focuses on identifying the resources required to set up and run CP programmes across Europe, and the cost and key cost drivers of these programmes to identify lessons learnt for the use of CP for future pandemics.

HERC have used the UK as a test case to first establish the elements and framework for the model. They have worked closely with NHSBT to firstly map the pathways for collecting and manufacturing CCP, and secondly to identify the resources required at each stage in the pathway to provide CCP in the UK.

The UK had two phases of CCP collection: Phase 1 (between March 2020 and June 2020) using existing resources and Phase 2 (between June 2020 and March 2021) which required new infrastructure of additional staff, equipment, and space. The model was constructed to consider the different components embedded within activities in each phase, for example, the resources (staff, consumables, equipment and overheads) and costs of recruiting donors, phlebotomy, sample testing, plasma collection and manufacturing and storage. This level of detail was required for the top-down micro-costing analyses, using detailed information on resource use and unit costs at an organisational level, described in more detail within the HERC report provided within Appendix 8.

The next table provides a summary of the components of the CCP programme in the UK, and their associated costs in Euro purchasing power parities (PPPs). We present average costs from later periods in the programme, which will be more applicable to a future programme since lessons learnt from this pandemic would be taken forward for future use.

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Components of costs associated with the CP programme in the UK.

Component	Time period	Average cost over the time period (Euro PPP)
Marketing	20 Apr 20 - 14 Mar 21	99 per HT unit
Sample testing (in session)	2 Nov 20 - 14 Mar 21	279 per HT sample
Sample testing (off-session)	14 Jan 21 - 15 Feb 21	101 per HT sample
CCP collection	2 Nov 20 - 14 Mar 21	799 per HT unit
Manufacturing/storage	2 Nov 20 - 14 Mar 21	86 per HT unit

PPP, purchasing power parities.

Data collection questionnaires were later prepared to support the acquisition of data from 21 countries across Europe taking a top-down gross costing approach, using aggregate resource use items and costs at an organisational level. With the questionnaire, data from nine European countries were collected and then compared (Belgium, Finland, France, Italy, Norway, Portugal, Sweden, Switzerland and the UK). At the start of the pandemic, the infrastructure for CP collection was in place in France, Italy, Portugal, and Sweden, but not in the remaining five countries, where it took between three and 12 weeks to get the infrastructure required to set up.

These countries had marked differences in CCP collection, the scale of the collection, and methods of selecting and measuring high-titre (HT) CCP which contributed to the variation in expenditure observed. The Table below reports the total costs per HT CCP donation and HT CCP unit for available countries across Europe. Estimates are very different, but what is included within costs also differs (further details in Appendix 8). Costs are significantly lower in countries where the infrastructure for apheresis plasma collection was already in place at the start of the pandemic.

HT donation and HT CCP unit costs based on the total costs of the programme.

Country	A	B ^a	D	F
Cost (Euro PPP) per HT donation	265	-	3409	2354
Cost (Euro PPP) per HT unit	265	198	1749	807
Pre-existing Infrastructure	Yes	Yes	No	No

PPP, purchasing power parities

^a Estimate PPP, purchasing power parities based on cost per HT CCP unit provided, rather than the total costs of the programme and total units produced.

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The summary of findings across the UK and Europe described in more detail within the report in Appendix 10 is as follows:

- 1) The cost of an HT CCP unit in the UK was 40% lower during Phase 2 of the CCP programme compared to Phase 1.
- 2) The key driver of costs was activities required for the collection of HT CCP; an area that needs to be optimised.
- 3) Testing samples first before CCP collection with the provision of home testing kits could reduce the costs of this component by two-thirds.
- 4) The scale of CCP programmes and their costs vary significantly.
- 5) Costs were lower in countries where the infrastructure for apheresis plasma collection was already in place at the start of the pandemic.
- 6) The cost is also determined by the ability to repurpose CCP, not reaching the therapeutic threshold, for general medical use including fractionation.

Considerations for the future

Costs are very different if countries have ongoing plasma collection programmes that can be built on, rather than starting a programme from scratch. Many countries now have such programmes, for example, the UK now collects plasma for medicines, so countries may be starting from a different place in a future pandemic.

Average costs of HT CP will likely change over the early stages of a CP programme, as countries learn how best to run a CP programme, and improvements are made over time. For example, in the UK it became clear that collecting large volumes of CP first and then testing is more expensive than first testing a small blood sample from donors for high levels of neutralizing antibodies (nAbs); testing was used to increase the proportion of donations that were HT, thus improving efficiency. Later more efficient ways of testing (home kits) were introduced, so the programme evolved again. The volume of CP collection was also a key driver of average costs in different periods. As programmes evolve, it is not straightforward to separate the cost of establishing a CP programme from the cost of production of CP (and it was not possible to do this from the data collected via the questionnaire).

The quality of HT CP produced will impact its effectiveness and costs. HT is subjectively determined, and through the pandemic, there have been cycles of re-evaluating the threshold for nAb potency. Analyses in WP4 have shown that there is not a linear relationship between nAb potency and nAb titre across different countries and laboratories. For example, two countries using a neutralising titre of 1:40 and 1:100, both had a nAb potency of 108 IU/ml, yet another region with a neutralising titre of 1:80 had a nAb potency of 409 IU/ml. There is a significant variability in the assays used to assess neutralisation and/or antibody content and so the estimates of antibody potency of CP. Therefore, it was not possible to modify the estimated costs of HT CP using the normalisation factors from WP4, which would have standardised that aspect of the HT CP unit costs, making costs from different countries more directly comparable.

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Another aspect of the quality of HT CP is pathogen reduction, which aims to reduce the passing on of infection to recipients and is an additional cost to the manufacturing of CP. However, pathogen reduction limits the ability to repurpose CP - pathogen-reduced CP can only be repurposed for clinical use (as is done in France and Belgium), it cannot be sold for fractionation or diagnostics. Countries which do not undertake pathogen reduction (Finland, Norway, and the UK) also have the option to repurpose CP and recoup some of the costs of manufacturing CP. Indeed, the UK recouped 2.6% of the total costs of its CP programme by selling plasma for repurposing (which is factored into the costs presented above), so this is a consideration for future pandemics. France, Italy, Portugal, Belgium, Sweden and Switzerland use pathogen reduction, so repurposing for fractionation would not be an option for them. However, repurposing of CP for general clinical use, if the neutralising antibody level was below the threshold or the unit was nearing the end of its shelf-life was an option used widely, particularly in France. In France, 44% of the cost to produce a CCP unit was recouped if it was not used as CCP for the reasons described above. Indeed, it should be noted that if the UK had been able to sell these CP units before expiry as standard plasma for direct clinical use, it would have generated 1.5 times more income than was recouped from repurposing the plasma for fractionation.

A challenge with these analyses was the availability of data. It was difficult to collect detailed data in the UK once the initial and larger programme had shut down and many staff had moved on to different roles. Many services across Europe completing the questionnaire reported difficulties obtaining all the information requested, which was reflected in the level of missing data on returned questionnaires, and the response rate of 43% (9/21 countries). In any future pandemic, efforts should be made to record and retrieve such data to facilitate economic analysis of plasma collection.

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Task 5.3 Perform SWOT assessment to support future SoHO development

Task leader: NHSBT; Contributing partners: All partners (Task leader NHSBT responsible)

What has been done

The strengths, weaknesses, opportunities and threats associated with CP's production and distribution have been updated from what was presented in the previous interim report. The grid below provides an outline of these.

SWOT analysis to support the use of convalescent plasma in future pandemics

STRENGTHS	WEAKNESSES
1. ACCESSIBILITY An intervention that is available quickly in countries that routinely collect plasma used for clinical use or fractionation. 2. AFFORDABILITY Less expensive than the alternative; commercially produced monoclonal antibodies or anti-viral drugs. 3. FUTURE PROOF Provides specificity to new and emerging infections or variants of these when CP is collected from donors previously infected with more recent viral variants and/or with boosted vaccination.	1. STANDARDISATION OF HIGH-TITRE UNITS- The parameters for selection of units with nAb titre suggested that the top 10% of CP collected can differ between blood establishments (see Task 5.4 below). Available equipment and expertise could be absent. The nAb in CP should demonstrate the ability to neutralise the variant in circulation, but it may be difficult to get test results of nAb activity against variants in a timely manner. Access to sequencing data on most recent variants could be unavailable or delayed due to varied capacity to sequence in different jurisdictions. 2. SITES AND RESOURCES to measure nAb titres to ensure agreement in a dose of CP used by different nations requires continued development. 3. INABILITY TO RESPOND QUICKLY TO NEW THREATS IN SOME JURISDICTIONS due to a lack of flexibility and expertise. 4. LARGE VOLUMES of high titre CP (>600mL) may be required and these volumes should be collected if possible and as equipment and protocols for plasma collection allow. 5. LIMITED TRANSFER OF CP due to different competencies of blood establishments in Europe. 6. LACK OF PATIENT OUTCOME DATA linked to CP titre on registry due to:

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	(a) LACK OF GDPR GUIDANCE for clinical trials and the subsequent difficulty to obtain patient outcome data. (b) NO DESCRIPTION OF PLANS TO SHARE DATA on consent forms so that obtaining patient data was more difficult (c) INABILITY TO RAPIDLY UPLOAD PATIENT DATA from 100-1000 patients at a time. (d) NO NORMALISATION OF THERAPEUTIC ANTIBODY LEVELS in CCP used for trials until later in the pandemic 7. UNDERPOWERED ANALYSIS OF CRUCIAL PATIENT SUBGROUPS WHEN RCTs NEED TO BE STOPPED EARLY. Difficult because the introduction of interim analyses can produce bias.
OPPORTUNITIES 1. PREVENTING LIFE-THREATENING DISEASE in populations that cannot generate their immune response or populations with pre-existing conditions that increase the risk of severe disease. 2. COMMUNICATING EXPERTISE THROUGH SUPPORT-E NETWORKS where methods of standardisation, new donor testing strategies, systematic reviews, clinical trials and economic analyses are performed. 3. SHARING CP-EXPERTISE TO LOW INCOME COUNTRIES WORLDWIDE where implementation of safe CP collection programmes are needed when access to safe and effective vaccines is not possible. 4. DEVELOPMENT OF STRATEGIES TO COLLECT CP FOR FUTURE VARIANTS. 5. DEVELOPMENT OF GUIDELINES FOR COLLECTION OF CP to ensure blood establishments will be ready for future pandemics. 6. STRUCTURED CP COLLECTION PROGRAMMES by different blood establishments.	THREATS 1. REDUCED CENTRAL FUNDING leading to loss of momentum required for completing RCTs. 2. SEASONAL VARIATION OF INFECTION and reduced recruitment to RCTs when rates of infection drop in warmer months. 3. MONOCLONAL ANTIBODIES (mAbs)- can provide therapeutic antibodies at very high concentrations potentially 100-fold greater than the same volume of CCP. However, the expense of mAbs prohibits their use and they do not provide a quick solution to protect or treat infections with new variants. Indeed, the narrow specificity of such therapies results in loss of efficacy against subsequent variants. 4. ANTI-VIRALS- The efficacy of those used for coronaviruses is varied and resistance to this class of drugs may occur. There are also complex drug interactions notable after transplantation which may limit the use of specific antivirals.

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7. BOOSTER VACCINATIONS to increase antibody titres in plasma from donors known to provide high titre CP. 8. PROVISION OF LOW-TITRE PLASMA FOR OTHER PURPOSES. Costs of CP collection could be offset by the use of plasma for other purposes, such as plasma for clinical use, fractionation or diagnostics. 9. PROVISION OF HIGH-TITRE CP FOR IVIG. Hyperimmune IVIG is a concentrated product from CP that may eventually protect immunocompromised patients. 10. DEVELOPMENT OF PLATFORM TRIAL(S) FOR FUTURE PANDEMICS to ensure rapid implementation of trials that will be ready for future pandemics to cover many different clinical scenarios while allowing diversity of approaches in different jurisdictions and by different clinicians. 11. DATA COLLECTION ON CP OUTCOMES FROM HOSPITALS. 12. STRENGTHENING LINKS WITH EXTERNAL HEALTH AGENCIES.	
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Task 5.4 Develop recommendations for CCP collection

Task leader: NHSBT; Contributing partners: All partners (Task leader NHSBT responsible)

What has been done

Activities within Work packages 3 and 4 support screening donors using validated high throughput serological assays to collect CCP-units taking donors with the very highest nAb concentrations. At the start of the pandemic, many services took those donors who had been hospitalised with COVID-19 and who had greater than the 90th percentile or above the top 10% of neutralising activity. Later in the pandemic, many services pre-screened donors, and measured nAbs against new variants.

SUPPORT-E has not specifically evaluated the production of CCP from donated whole blood because it considers plasmapheresis the recommended way of collecting CP which optimizes the efficiency and frequency of collections, avoids unnecessary red cell loss in the donor and optimizes the volume of plasma that can be generated for use.

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However, CCP can be prepared by processing whole blood in the instances of routine whole blood donation from a previously infected person, especially if there is no plasmapheresis program in place, provided that the resulting erythrocytes can be used for therapeutic purposes. The main limitation of such CCP obtained from whole blood is the possibility of donating whole blood every 3 months and that it can only be used for one patient for one transfusion.

Transfusion of whole blood to provide CCP infusion is not recommended.

To achieve collection of plasma with very high nAb concentrations throughout the pandemic the following is recommended:

- a) A central repository for equal access to viral sequences to facilitate the engineering of viral recombinants to improve the rate at which the serological assays are validated against functional assays.
- b) Co-ordinated collection of CCP to form plasma pools and standards from at least 30 donors that have been infected with the most recent SARS-CoV-2 variant.
- c) A central processing laboratory that provides the standard to testing laboratories in each jurisdiction to identify thousands of high titre CCP units across Europe.
- d) Early preparedness to develop serological assays with a wide dynamic range essential for CCP collected from vaccinated donors.
- e) A validated serological assay should be easier to standardise between laboratories than neutralisation assays provided the features of equipment used in the testing laboratories are the same. This would ideally reduce the need for harmonisation factors.

Task 5.5 Develop recommendations for CCP use to treat COVID-19

Task leaders: NHSBT and EFS; contributing partners: EBA, RKV, DRK-BSD, IRCSS, ASST MANTOVA, ISS-CNS, SRK.

What has been done

Following the use of Preliminary Guidance Documents developed by Workpackages 1 and 2 to define the criteria for the selection of clinical trials (both randomised and non-randomised) (Task 1.2) and monitored access programmes (Task 1.3), there were no new trials addressing areas identified by the GAP analysis.

The most valuable part of this analysis has been to identify patient groups and clinical situations where there is a trend towards benefit but, as yet insufficient evidence to make a policy recommendation or clinical guideline. Crucially, trials providing sufficient information to make well-founded evidence-based policy were limited in the following areas:

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- (i) early treatment with CCP in patients with COVID-19 but not yet hospitalized
- (ii) treatment with high-titre CCP;
- (iii) targeted inclusion of patients at particular risk for developing severe COVID-19 disease, notably immunocompromised patients unable to respond to vaccination;
- (iv) impact of SARS-CoV-2 variants on the efficacy of CCP collected at different time points throughout the crisis.

Indeed, the Cochrane Living Systematic Review (LSR) had, as part of Workpackage 5, identified that CCP should not be given to patients who have been hospitalised with COVID-19 and who have already developed detectable antibodies to the virus. Although this is a negative result from the view of patient benefit, it is a very important result for guiding policy by avoiding inappropriate collection and use of CCP. The review also identified sub-groups in which more information from clinical trials was required:

-Patients who are treated early in the course of the disease as outpatients (Appendix 2)

-Patients who are immunocompromised (Appendices 3 and 5)

Importantly, the sub-group analysis of data from trials within the living systematic review that compare early treatment with later treatment or the presence of anti-SARS-CoV-2 antibodies at the time of treatment and also the data from the monoclonal antibody arm of the RECOVERY trial (RECOVERY Collaborative Group, 2022) all suggest that in future trials the time of treatment in relation to the onset of the disease and the serological status at the time of treatment should be used as indicators for treatment with CCP.

Activity since the interim report in June 2022 has focussed on obtaining high-quality evidence to identify the patient groups that will benefit from the use of very high-titre CCP to treat COVID-19. High-titre CCP comprises a high concentration of polyclonal antibodies that are better able to target new viral antigen epitopes than monoclonal antibodies. To this end, the Randomized Open-Label Trial of Convalescent Plasma Therapy in Clinically Vulnerable Individuals with Mild COVID-19” (COVIC-19) (Desmarets et, 2023) from within SUPPORT-E focussed on:

- Early treatment with CCP (within 3 – 7 days after the onset of symptoms in patients with mild COVID-19) (without need for hospitalization for COVID-19).
- Administration of high-titre CCP exceeding a pre-specified threshold of anti-SARS-CoV-2 antibodies from super-immunized individuals (i.e., immunized by a SARS-CoV-2infection + a vaccination).
- Treatment of vulnerable patients who are at high risk of progression to severe COVID-19.
- Analysis of variants causing the infection in the trial patients (by SARS-CoV-2 whole genome sequencing) and *in vitro* studies on cross-neutralization using high-titre CCP from vaccinated, convalescent donors against these variants (Seidel, et al., 2023).

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COVIC-19 has now completed recruitment and its results are available in a pre-publication archive (Hoffmann et al, 2024).

COVIC-19 assessed CCP in immunocompromised patients (n=120) with mild COVIC-19 in 10 clinical trial centres across Germany, France and the Netherlands. Patients were randomized 1:1 to receive either standard of care (SoC) alone (SoC group) or SoC and 2 units of CCP. Most patients (86%) had received ≥ 3 SARS-CoV-2 vaccinations. The primary endpoint was hospitalization for progressive COVID-19 symptoms or death by day 28 after randomization, analysed on a modified intention-to-treat basis (117 patients). The safety analysis included the full analysis set.

Participants in the CCP group received a median of 559 ml CCP from convalescent, vaccinated donors with very high levels of SARS-CoV-2 antibodies (median 81,810 IU/ml) 4 days after symptom onset. The primary outcome occurred in 5/58 patients (8.6 %) in the SoC group and in 0/59 patients (0 %) in the CCP group, difference -8.6 % (95 % confidence interval of difference -19% to -0.80%; p-value 0.027; Fisher's exact test). The course of SARS-CoV-2 antibodies in the patients demonstrated a passive transfer of antibodies by the CCP, in particular neutralizing effects against new SARS-CoV-2 variants. Whole genome sequencing of SARS-CoV-2 in patients during follow-up showed significant intra-host viral evolution, but without differences between groups. CCP was well tolerated. This study showed early administration of high-titre CCP can prevent hospitalisation or death in immunocompromised patients with mild COVID-19.

A second multi-centre randomised trial, REMAP-CAP was restarted to also determine if very high titre CCP could be used to prevent severe disease in immunocompromised patients testing positive for COVID-19 after admission to hospital. Recruitment to this trial has been slow but recruitment is continuing with sites open in Australia, Canada, France, Netherlands and UK. An interim analysis is expected in Spring 2025.

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Task 5.6 Recommendations for future outbreaks of SARS-CoV-2 or other novel pathogens

Task leader: NHSBT; Contributing partners: EBA, EFS, RKV, DRK-BSD, IRCSS, ASST MANTOVA, ISS-CNS, SRK (Task leader NHSBT responsible)

What has been done

We have evaluated observations from a systematic review of trials using CCP to treat vulnerable patient groups and the experience from the COVIC-19 trial. This has been used to provide the learning points and recommendations listed here.

5.6.1 Recommendation 1: The Pandemic and the Funding Response

5.6.1.1 KEY LEARNING POINTS

- a) Unprecedented collaboration across blood services was achieved by a rapid response by funders.
- b) The network of clinicians and scientists across Europe with expertise in systematic reviews, epidemiology, immunology, virology, and clinical trials allowed CP therapies to be tested and evaluated.
- c) The pandemic and the responses needed evolved rapidly.
- d) Future pandemics are likely to have different epidemiology, clinical features and responses to immunological, chemotherapeutic therapies and adjunctive medical care.

5.6.1.2 RECOMMENDATIONS

- a) Support network of blood services and other experts to allow collection, testing, analysis, and trials of high-titre CP.
- b) Establish expert and timely review of research proposals.
- c) Maintain responsive and flexible funding as the pandemic evolves.
- d) Continue funding while valid and relevant scientific and technical questions remain to be answered.

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5.6.2 Recommendation 2: Collection of data on CP use

5.6.2.1 KEY LEARNING POINTS

- a) The quality and utility of international data outside clinical trials have been of limited value because of restrictions on the use of personalised data and the many confounding factors that influence outcomes, including clinical status and pre-existing conditions of patients, demographic factors, viral variants and adjunctive care.

5.6.2.1 RECOMMENDATIONS

- a) Further work is needed to complete the analysis of existing data
- b) Further work is needed to establish what data should be collected in future to maximise the value of the data
- c) Establish a national and/or European collection system of relevant and comparable data on CP production and use early in the pandemic.

5.6.3 Recommendation 3: Reviews

5.6.3.1 KEY LEARNING POINTS

- a) A very significant amount of work by an expert team was needed to continuously review and analyse clinical trial data from hundreds of international clinical trials.
- b) The systematic literature reviews on the use of CP have been a very valuable resource for national and international authorities, blood services and clinicians.

5.6.3.2 RECOMMENDATIONS

- a) Establish systematic reviews for continuous analysis of the efficacy of monoclonal and polyclonal antibodies in randomised controlled trials for prophylaxis and therapy of pre-hospital, hospitalised and ICU patients.
- b) Establish expert and timely review of recommendations for the use of CP (and other therapies).

5.6.4 Recommendation 4: Collection of CP

5.6.4.1 KEY LEARNING POINTS

- a) Rapid and large-scale collection of CP is possible and practical.

5.6.4.2. RECOMMENDATIONS

- a) We recommend that if apheresis plasma production infrastructure already exists, then this should have the capacity to upscale production to meet the demand for CP.
- b) A sample-first policy is more cost-effective than collecting plasma and then testing to assess if high titre.
- c) Alternative uses for plasma that is not high titre should be sought – e.g., fresh frozen plasma (FFP), plasma for medicines (fractionation) or plasma for diagnostics if possible.

5.6.5 Recommendation 5: Testing

5.6.5.1 KEY LEARNING POINTS

- a) Many serological test kits were rapidly made available
- b) Only a few specialised centres were able to provide accurate assays of nAb.
- c) Establishing the relationship between different serological assays and accurate assays of nAb required international collaboration.

5.6.5.2 RECOMMENDATIONS

- a) Establish plasma standards that can be calibrated to international standards from WHO (World Health Organization) or NIBSC (National Institute for Biological Care).
- b) Establish reliable virological assays for nAb to new variant variants in a few centres that include rapid assessment of new viral variants.
- c) Establish calibration between the different high-throughput serological available tests to enhance the resilience of the supply of testing kits.
- d) Provide quality control scheme and reagents for serological assays.

5.6.6 Recommendation 6: Clinical Trials

5.6.6.1 KEY LEARNING POINTS

- a) Randomised controlled trials have provided the most reliable data for the efficacy of CP.
- b) There is some, but not conclusive evidence, that early use of high-titre plasma may produce better clinical outcomes.
- c) There is some, but not conclusive, evidence from trials that patients who are immunocompromised or who are seronegative benefit from CP.
- d) Initial evaluation of CP should focus on the transfusion of high titre CP:
 - a. early after symptoms start in vulnerable patients and
 - b. throughout the course of the disease in immunocompromised patients

5.6.6.2 RECOMMENDATIONS

General

- a) Encourage and maintain international trial platforms for testing of CP.
- b) Support countries and sites to open sites for international trial platforms for example COVIC-19 and REMAP-CAP to gather definitive evidence as quickly as possible.
- c) Encourage enrolment of all patients receiving CP into adequately powered large-scale trials to examine the use of CP prophylaxis and therapy of pre-hospital, hospitalised and ICU patients.
- d) Establish analysis of trials for sub-groups based on the most vulnerable groups, for example in this pandemic, older age, pre-existing disease, immunocompromised patients, and negative serological status.

Specific recommendations for the use of COVID-19 convalescent plasma updated in December 2025

- e) Should CCP transfusion be provided for infection prevention (i.e., for individuals with close contact exposure to a person with COVID-19 but who are not yet infected)?**

We suggest **against** using prophylactic CCP transfusion for uninfected individuals with close contact exposure to a person with COVID-19 (weak recommendation, low certainty evidence).

We cannot make a recommendation for immunocompromised patients – insufficient data.

- f) Should CCP transfusion be provided in addition to the usual standard of care to outpatients with COVID-19 who are at high risk of disease progression?**

Early administration of high-titre CCP may prevent hospitalisation or death in immunocompromised patients with mild COVID-19 (weak recommendation, low certainty evidence).

We suggest additional work is required to assess the health economics of using CCP transfusion in addition to the usual standard of care in patients who are immunocompromised.

In the early stages of a pandemic, clinical trials should investigate whether CP transfusion is effective in addition to the usual standard of care to outpatients who are at high risk of disease progression.

5.6.6.2 *RECOMMENDATIONS continued*

g) Should CCP transfusion be provided in addition to the usual standard of care for inpatients with COVID-19?

We recommend against using CCP transfusion in addition to the usual standard of care for seropositive inpatients with COVID-19 who have antibodies against the virus (strong recommendation, high certainty evidence).

Available data suggests that CCP transfusion of immunocompromised (or seronegative) patients hospitalised with COVID-19 could be beneficial. However, due to insufficient data, we cannot provide a definitive recommendation for the use of CCP to treat immunocompromised (or seronegative) patients hospitalised with COVID-19.

In a future pandemic, clinical trials should address the efficacy of very high titre CP in immunosuppressed patients, as well as early administration in vulnerable patients (before vaccination is available), as a matter of priority.

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