Support-e

SUPPORTing high quality evaluation of covid-19 convalescent plasma throughout EUROPE

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SUPPORTING HIGH QUALITY EVALUATION OF COVID-19 CONVALESCENT PLASMA THROUGHOUT EUROPE

Reporting period: **July 2021 - June 2022**

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To all Support-ers

The second half of the duration of the SUPPORT-E project was marked by the dynamic development of the pandemic, the emergence of new variants, the spread of vaccination and a series of findings related to the use of **COVID-19 convalescent plasma (CCP)**. This flow of data and information allowed us to meet most of the project objectives on time, while some others required data on the clinical use of CCP that became available late in the project. Based on several assessed knowledge gaps, we identified the need for an **additional clinical trial** to achieve the project's objectives and provide high-quality evidence to define the effective use of CCPs in the treatment or prevention of COVID-19. To achieve this, we supported a randomized, open-label trial of convalescent plasma therapy in clinically vulnerable individuals with mild COVID-19 (COVIC-19) with a planned completion later than the end of the SUPPORT-E project. Therefore, the European Commission (EC) approved the **extension of the project for 12 months** to enable the inclusion of study results in the conclusions of our project. We are grateful to everyone who contributed to obtaining the extension, including the EC. In addition to the completed project tasks, the results of the **COVIC-19** study will clarify existing knowledge gaps so that the final project report and recommendations can comprehensively cover the use of CCP for the treatment of COVID-19 and provide a baseline for the use of convalescent plasma in future outbreaks or pandemics.

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Pierre Tiberghien

About SUPPORT-E

(SUPPORTing high quality evaluation of COVID-19 convalescent plasma throughout Europe)

The main goal of the SUPPORT-E project is to provide support to high quality clinical evaluation of COVID-19 Convalescent Plasma. After an accurate analysis of the data collected also through the EU-CCP database, SUPPORT-E team will proceed to achieve a consensus on the appropriate use of CCP in the treatment of COVID-19 across Europe. Ultimately, the team will share its findings on the effectiveness of CCP as a therapeutic option to tackle COVID-19 and put forward evidence-based recommendations to be applicable throughout Europe in the current and potential epidemiological outbreaks.

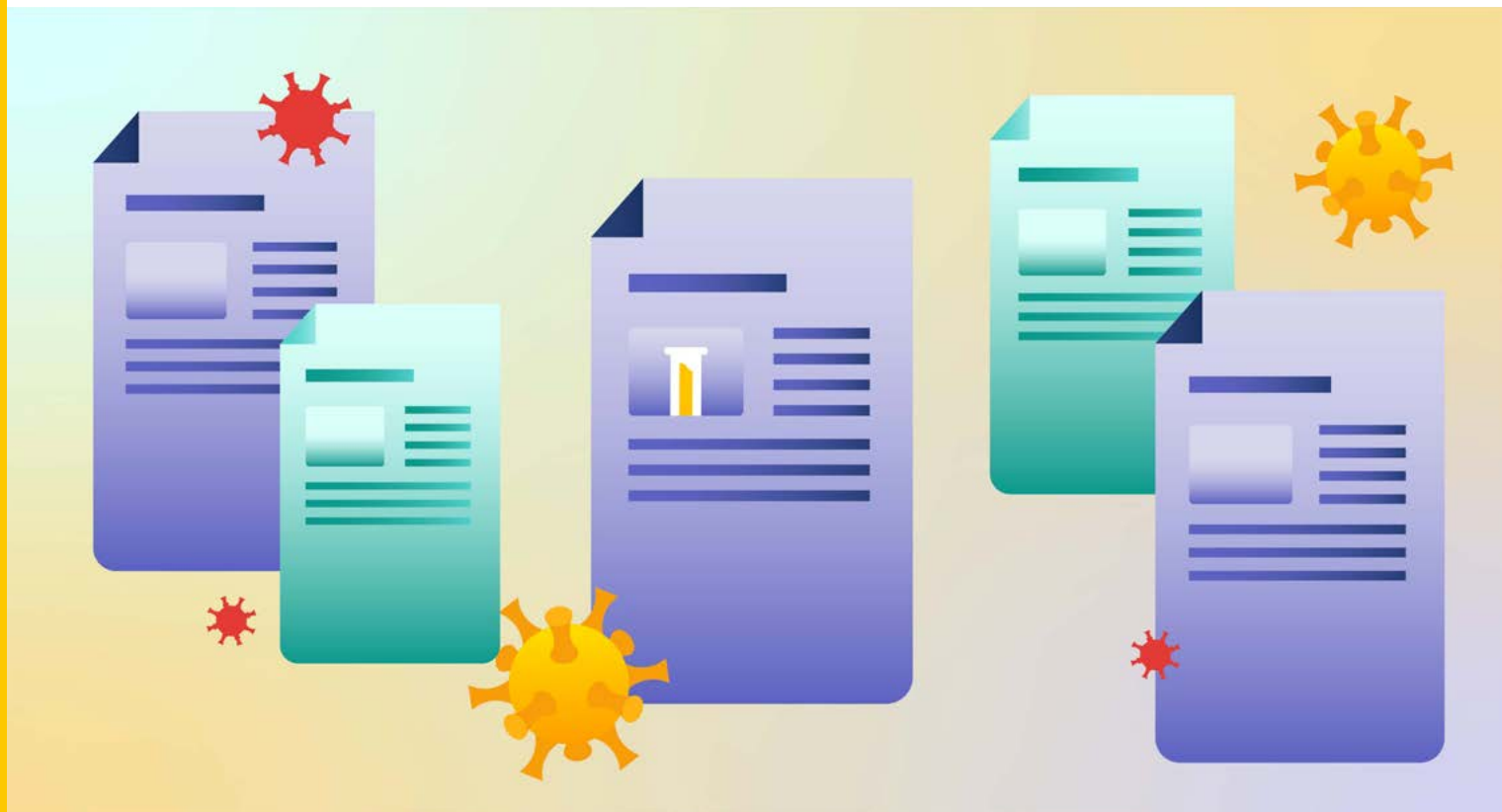
The team is represented by the **SUPPORT-E Consortium** that is composed of 12 partners under the leadership of the European Blood Alliance, the association of not-for-profit Blood Establishments (BEs), with 26 members throughout the European Union and EFTA States that overall manage 17 million blood donations per year.

About CCP

CCP is plasma collected from donors that have recovered from COVID-19 and contains antibodies that could neutralise SARS-CoV-2 infection. Transfusion of CCP may improve the disease course of patients with COVID-19.

About EU-CCP Database

The European Commission is working together with the Member States, the European Blood Alliance (EBA) and the SUPPORT-E Consortium to provide a platform to support the study of CCP as a treatment option for COVID-19 patients. The open-access database gathers and makes available data on CCP donations and patient outcomes following transfusion with CCP. It includes data from European blood establishments on CCP donors, CCP donation, CCP collection and CCP antibody content as well as patient outcome data from clinical trials and monitored access use. The database is intended to consolidate evidence on the safety and effectiveness of CCP donation and of CCP therapy in European donors and patients.



GLOSSARY

Clinical trials
Studies performed to investigate the safety and/or efficacy of a medicine. For human medicines, these studies are carried out in human volunteers.

Monitored access use
The use of an unauthorised medicine outside a clinical study in individual patients under strictly controlled conditions. This helps to make medicines that are still under development available to patients.

Plaque Reduction Neutralisation Test (PRNT)
A manual laboratory test used to estimate the titer of antibodies in CCP that neutralizes SARS-CoV-2 infection.

Microneutralisation (MN) assay
A semi-automated laboratory test to quantify the titer of antibody in CCP that neutralizes SARS-CoV-2 infection.

Enzyme-Linked ImmunoSorbent Assay (ELISA)
A semi-automated laboratory test to quantify specific antibodies in CCP..

Strengths, Weaknesses, Opportunities, Threats (SWOT) Analysis
A tool for strategic assessments used to help an organisation to identify strengths, weaknesses, opportunities and threats related to project planning.

Substances of human origins (SoHO)
Substances like blood and blood components, tissues and cells.

Gap Analysis
A particular kind of analysis that involves the comparison of actual performance with potential or desired performance..

WP 7 PROJECT MANAGEMENT

WP 6 DISSEMINATION AND EXPLOITATION

WP 1 REVIEWS OF ONGOING AND UPCOMING CLINICAL TRIALS

WP 2-3 ANALYSIS OF DATA COLLECTED IN EU-PLASMA-DATABASE

WP 4

DEVELOPING, CALIBRATING AND STANDARDISING NEUTRALISATION ASSAYS FOR THE CCP DONOR SELECTION

WP 2

COVIC-19 – PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF COVID-19 CONVALESCENT PLASMA IN THE TREATMENT OF COVID-19

The team will use only high antibody titre CCP and patients will be elderly, younger with co-morbidities, immunosuppressed patients.

WP 5

PRODUCE RECOMMENDATIONS ON CCP COLLECTION, CCP USE TO TREAT COVID-19, CONVALESCENT PLASMA USE TO TREAT NOVEL PATHOGENS

UPDATED RECOMMENDATIONS BASED ON THE RESULTS OF COVIC-19 CLINICAL TRIALS

WP 1 – Assessing CCP, conducting clinical evaluation and defining best practices

WP1 work focused mainly on the clinical evaluation of the most relevant clinical trials and monitored access programmes on CCP. To achieve this objective, an extensive electronic literature and guidelines search was performed in the major online databases.

For this task were reviewed:

- **18,218 articles**
  - 314 considered relevant
- **4,854 clinical studies**
  - 227 considered relevant
- **11,084 monitored access studies**
  - 200 considered relevant

Following this screening, a series of characteristics and practices of the various European and Non-European protocols were collected and then assembled into a document that list the **criteria for a high quality evaluation and selection** of clinical trials and monitored access programmes. These criteria were split into five sections (Study Selection, Donors Selection, CCP Selection, Patients Selection, Donors and Patients Adverse events) and were also classified for their degree of priority (mandatory, recommended, optional).
After these assessments, WP1 team produced preliminary guidelines for the selection of high-quality clinical trials and monitored access programmes worthy of financial support.

Since the emerging of COVID-19 variants and the increasing diffusion of vaccination campaigns, WP1 team changed the keywords for their constant work of monitoring all the **literature on CCP**, in order to keep this search up to date. This updated systematic analysis of the literature proved that the interest in the curative properties of CCP in different settings, especially in immunocompromised patients, remains high.

WP 2 – Supporting high quality clinical evaluation and producing data-sets for inclusion in the database

After collaborating with WP1 in drafting the preliminary guidelines for selection of high quality clinical trials on CCP, WP2 contacted these trials to verify their availability to collaborate with SUPPORT-E, including the data they had collected in the EU-CCP Database. In the early stages the trials teams outreached were 27 (18 randomized trials, 9 non-randomized trials respectively).

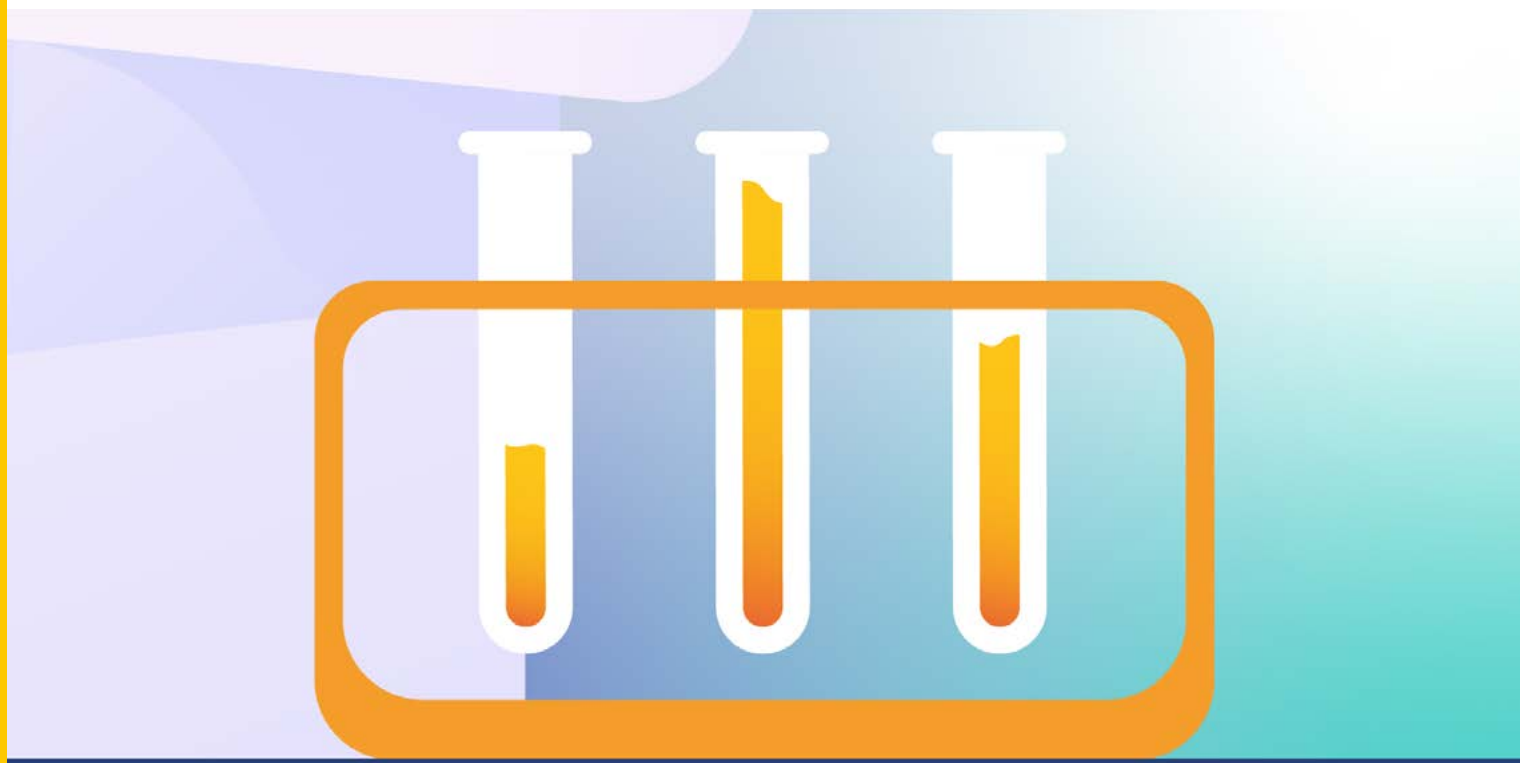
At the time of this report the trials contected were:

- **42 trials**
  - 28 randomized
  - 14 non-randomized

A **gap analysis** was performed and regularly updated on all the information provided by the selected trials. The analysis established that the data collected did not provide information on a combined approach regarding the following aspects:

1. **Early treatment with CCP in patients not hospitalized due to COVID-19.**
2. **Treatment with high-titre CCP.**
3. **Targeted inclusion of patients who are particularly at risk for developing severe COVID-19 disease.**
4. **Impact of SARS-CoV-2 variants on the efficacy of CCP.**

So the SUPPORT-E Consortium decided to develop and implement the clinical trial **“Randomized Open-Label Trial of Convalescent Plasma Therapy in Clinically Vulnerable Individuals with Mild COVID-19”** (COVIC-19)”, in order to fill all the gaps in data collected by previous trials. COVIC-19 started its enrolment in Germany and the Netherlands and will soon be extended in other countries, e.g. **France**. WP2 also provided information and support to representatives of other clinical trials groups and reached out to many competent authorities and investigators to support the start-up of COVIC-19 in other clinical trials sites.



WP 3 – Govern the EU-CCP Database

The EU-CCP database has been developed by the European Commission (DG SANTE, DG DIGIT, and DG CNECT) in collaboration with EBA and has been managed jointly by EBA and the European Commission. The Activities within this work-package focused on addressing management of the database, quality and monitoring of data, improvements of IT tools for accessibility, uploading of data, generating regular dashboards, accrual monitoring and analysis. During the early stages of the project, WP3 team defined that the following types and categories of data would have been collected by Blood establishments (BE):

1. **CCP collection policy and strategy for each BE.**
2. **Donation data – CCP collection and product characteristics.**
3. **Patient data - use of the CPP and clinical follow-up of recipients.**
4. **Data modelling and database structure.**

Then the WP3 team has been working diligently since the beginning of the SUPPORT-E project to liaise with the BEs who have registered to the EU CCP Database to receive feedback on how to optimise the registration process as well as on the submission of data.

As of June 2022,

- **More than 166.000 plasma donations** of COVID-19 convalescent donor from over 70 European BEs were recorded.

The database also made it possible to collect data related to

- **2.914 patients** (from 9 contributing countries), who had received CCP during their treatment.

The main obstacle to the collection of these data were related to the interpretation of General Data Protection Regulation (GDPR) and the reluctance of clinical teams to send patient data to a publicly accessible database. All data were assessed for quality, data safety and curated in function of analysis purposes, generating repositories and reports. Initial analyses are ongoing, mainly on donations data, where numbers allow statistical analysis. Additional efforts are focusing on carrying out a second analysis of the data received so far on donations, patients and plasma.

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Thus, the following tasks are yet to undergo final analysis:

Safety assessment of donor collection and recipient use

We will assess severe adverse events associated with CCP treatment among recipients in the final dataset.

Relation between Ab characteristics and donor characteristics

We will assess the associations between donor characteristics and plasma antibody concentration and activity.

Time of administration and disease severity

We will link time of administration relative to diagnosis with risk of mortality and chance of cure.

WP 4 – Improving plasma potency assessment

For those who had access to laboratory tests for virus neutralization and/or antibody content (ELISA), the nature and standards of available assays were unclear. In the early stages of the project, WP4 focused on establishing an inventory for access to and nature of antibody testing across the EU.

- The WP4 team conducted a survey among the **EBA associated blood establishments (26)** and the principal **investigators of clinical trials (20)**.
- Then, after an evaluation of the **29 answers received**, WP4 team constructed and distributed **a panel of a centrally prepared and characterized CCP samples** to calibrate laboratory tests.

This allows to compare laboratory test results across different assays used in different clinical trials. WP4 provided support for SARS-CoV-2 testing to laboratories without access to testing. In addition, the performance of laboratories in testing for anti-SARS-CoV-2 antibodies was compared across 12 European laboratories (UK, Denmark, Norway, the Netherlands, Belgium, Spain, Estonia, France and Slovenia involved in SUPPORT-E and convalescent plasma trials. This published work has helped to compare neutralising antibody content in plasma collected by different blood services across the Europe.

WP4 developed a novel ELISA-based laboratory test that can distinguish between neutralising and non-neutralising CCP Furthermore, WP4 compared commercially available **ELISA-based** assays with plaque reduction neutralisation test (**PRNT**) or microneutralisation (**MN**) assays. This analysis that resulted in many peer reviewed publications suggested that some commercially ELISA assays may perform effectively as surrogate assays or serve as a reliable proxy for neutralisation antibody titre, and it has also helped to determine the antibody threshold to CCP supplied to ongoing multi-country COVIC-19 trial.

WP 5 – Developing recommendations and preparing for the future

Data from patients enrolled in randomized clinical trials conducted globally between March 2020 and May 2022 was summarised by the WP5 team. A series of Cochrane living systemic reviews were published. The last publication within this reporting period, updated findings for patients with mild COVID-19; for patients with moderate to severe COVID-19; and for patients with moderate or severe disease that are seronegative or immunocompromised. The evidence did not show benefit of CCP for patients with severe to moderate disease, which was not helped by the different methods used to report outcomes. However, more evidence is still required to know if CCP is beneficial when used early before symptoms develop in populations vulnerable to severe COVID-19 disease. This has been addressed through implementation of the COVIC-19 trial in WP2.

The WP5 team, in collaboration with the **Health Economics Research Centre (HERC)** at the University of Oxford, also planned work to determine costs for the implementation of a CCP programme.

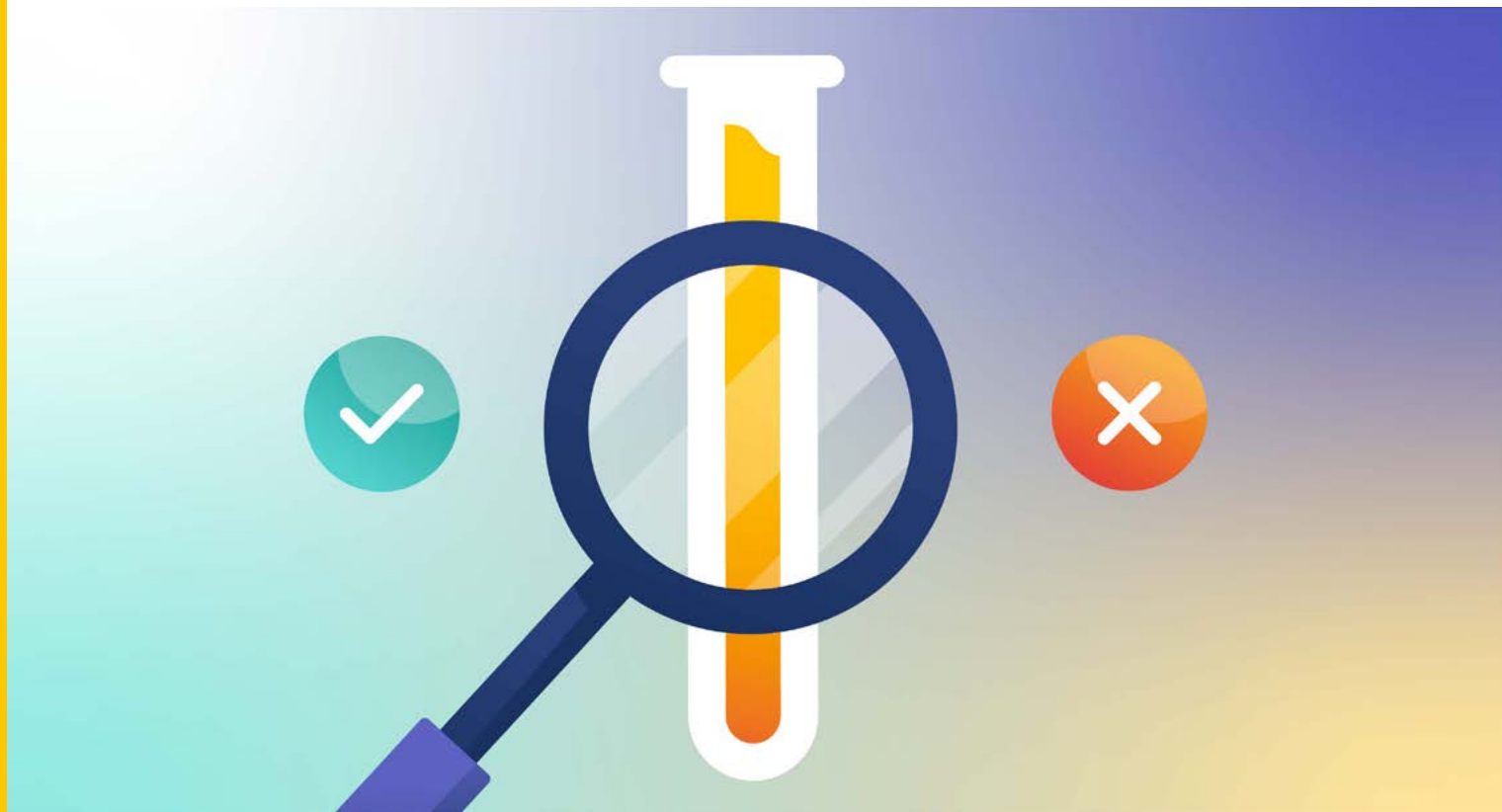
They compiled questionnaires to collect data from

24 Blood Establishments
across 20 different European countries.

The economic analysis that followed this survey suggests that collection of high doses of CCP with high concentrations of neutralising antibodies will be the main contributor to the expense of a CCP programme. They found that collecting large volumes of CCP first and then testing is more expensive than first testing a small sample for high levels of neutralising antibodies. Instead, off-site testing using home testing kits, could reduce costs associated with collecting high dose CCP. The production of CCP units may also require additional purchase of specialist apheresis equipment as well as the expertise and time of staff within the donor care and manufacturing departments.
This analysis will be updated in the coming months, taking into account data from additional European countries and the normalisation factor for testing at different sites.

A SWOT assessment was also performed, using input from WP1-4. This provided the basis for suggestions to improve the collection and utilisation of convalescent plasma (CP) to tackle pandemics in the future. Specifically, among other things, WP5 highlighted the necessity of:

1. **Uninterrupted central funding to allow rapid implementation of platform-based randomized trials.**
2. **The standardisation of methods to assess high dose CP to improve the interpretation of results between trials or across different sites within the same trials.**
3. **Continued monitoring of antibody concentrations in CP to ensure activity against the latest variants of the pathogen.**
4. **Repurposing the un-used plasma to offset the initial costs of CP collection.**



Recommendations

Within the 2021-22 timeframe, WP5 work focused on developing **three different sets of recommendations** on CCP collection, on use of CCP to treat COVID-19 and on use of CCP to treat future outbreaks of Sars-CoV-2 or other novel pathogens. Preliminary recommendations were based on observations within previous WPs and will be updated once COVIC-19 results are available.

1

Recommendations for CCP Collection

- CCP with the correct specificity and sufficiently high concentration of antibodies to neutralise the latest variant of SARS-CoV-2 is critical to the effectiveness of treatment. Confirmed by WP2 and WP3 using data provided by WP1 to identify the parameters that should be used to collect high titre CCP.

- CCP collected from convalescent donors vaccinated either before or after re-infection are more likely to provide very high dose CCP with sufficient neutralising antibodies against Omicron. Confirmed by work within WP2.

- Sample testing and collection of CCP should be no longer than 90 days after vaccination to efficiently collect CCP with the required concentration of neutralising antibodies. Confirmed by observations in WP2.

To manage collection of CCP as **new variants** of COVID-19 emerge:

- Continue to monitor very high dose CCP collected from vaccinated donors against new emerging variants because with each new variant there is incremental loss

of neutralisation efficacy in vitro. This will be addressed within WP2 as part of COVIC-19.

- Test samples from vaccinated donors re-infected with the latest variant in circulation. This will require close collaboration between the health authorities and the blood establishments to recall CCP donors quickly to test and collect CCP when appropriate. This will be continued within WP2 as part of COVIC-19.

- Adapt assays to achieve a greater dynamic range to accurately measure the very high antibody levels in CCP collected from vaccinated donors. The partners within WP2 will continue to monitor the suitability and adapt assays for plasma with high titre.

- Continue to review how different assays carried out in laboratories across Europe are standardised. This will be done through continued collaboration of partners within WP2 and WP4.

2 Recommendations for use CCP to treat COVID-19

Trials for early use of **very high dose of CCP** (from vaccinated CP donors) to treat vulnerable patients at high risk of progression to severe COVID-19 are recommended. These trials (such as COVIC-19) focus on treating specific target groups, i.e. clinically vulnerable elderly and immune-compromised.

Other recommendations include:

- Assessment of CCP within clinical trials to reduce the time taken to obtain high quality data. The Living Systematic Review has shown that it is difficult to obtain meaningful data without bias when CCP is used within monitored access programmes.

- Use of platform based registered clinical trials that are easy for hospital staff to follow and can be adapted to include new treatment groups and patient groups as new variants emerge. The Living Systematic Review has shown that platform based RCTs recruit enough participants that helps to identify patient groups that may benefit from CCP in the future.

- Access to patient records alongside the biological characteristics of CCP to better understand outcomes associated with CCP. Clear guidelines on how to apply GDPR when patient data is required for the development of new therapies during a pandemic are required.

- A database to record and stratify adverse events according to plasma and patient characteristics, as developed in WP3. This will provide a valuable reference for the Data and Safety Monitoring Committee of RCTs investigating the use of CP for COVID-19 and other novel pathogens in the future.

- Use of CCP that has standardised neutralising antibody doses or titres to allow comparison of outcomes between trials.

Thus, the following activities will be required:

- Use of calibration factors from WP4 to normalise titres and antibody ratios within the databases developed in WP2 and WP3. This will improve comparison of outcomes between trials and help to clarify if there is an association of antibody titre in CCP with clinical outcomes.

- Further work on the effector function of antibodies in CCP (other than neutralising titres) to understand their importance for viral clearance versus adverse events in patients.

3 Recommendations for future outbreaks of Sars-CoV-2 or future pandemics

On the basis of observations within this report period, WP5 recommends the following for use of convalescent plasma (CP) in future outbreaks of SARS-CoV-2 or other novel pathogens:

- To invite patients to enrol in RCTs that are sufficiently powered to test the effectiveness of the intervention rather than enrolling to monitored or compassionate use programmes.
- To provide continued preparedness through the establishment of platform-based trials that are designed to determine benefit of CP in specific patient groups early in the pandemic. Where feasible flexibility should be built into the design of the trial to allow changes of the patient population.
- To use standardised endpoints (e.g. time to event) within the trial design that will improve systematic analyses and comparison of results from different countries in Europe.
- To ensure that collection of high dose convalescent plasma is as efficient as possible so that it constitutes more than 65% of CP collected. Start home testing for antibody levels before collection of CP units within the first 2 months of the pandemic.

The recommendations for future outbreaks will be developed:

- Using additional health economics data from more blood establishments in Europe to improve accuracy of the budget for CP programmes in the future.
- By assessing the potential income when CCP that did not meet criteria for COVID-19 is repurposed for commercial use (e.g., fractionation).

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- Using interim results from registered clinical trials (COVIC-19 and REMAPCAP) that use very high doses of CCP (from vaccinated CCP donors) for early treatment of vulnerable patients at high risk of progression to severe COVID-19.

- To enable more efficient use of resources for combining data from different regions within Europe by including sites of excellence for training; standardisation of assays; and identification of new variants of concern or other pathogens.

WP 6 – Dissemination, exploitation and communication

In the early months WP6 team worked on the visual identity and on the dissemination and exploitation plan to raise awareness about the SUPPORT-E project and its results. The logo, the dedicated communication materials and the official website were created along with a p**romotional video** that showcase the project and call to action all potential CCP donors.

In the timeframe considered in this report, WP6 updated the dissemination plan. In particular, a specific modification was the inclusion of a new context in the Plan referred to the availability and efficacy of vaccinations. As per the media relations, three press releases were issued and a layman's version of the open letter to WHO "COVID-19 Convalescent Plasma should be further investigated" was produced and then disseminated in two specialized newsfeeds dedicated to science and health news, namely AlphaGalileo and EurekAlert.

WP6 team, in collaboration with European Blood Alliance, organised a meeting that was held in Rome on **17 June 2022**. The event was addressed to the project Consortium, EC representatives and some key stakeholders. The agenda of the meeting was structured in 4 sessions, 1 introductory and the other 3 technical. In particular, the technical ones foresaw a presentation of the activities carried out within the WPs followed by a discussion with the audience. Following topics were discussed:

1. **"Assessing CCP, supporting high-quality clinical evaluation and data collection";**
2. **"Plasma potency assessment and future preparation";**
3. **"Sustainability: European forthcoming perspectives about CCP".**

WP6 team also produced the project newsletters and the layman's versions of the interim and final technical reports.

WP 7 – Project management

European Blood Alliance, WP7 leader, ensured that project implementation by the partners has been compliant with the conditions set forth in the Grant agreement and the Consortium agreement. The Coordinators also led the registration of Blood Establishments on the EU CCP Database. Lastly, WP7 team, together with WP2 and WP5 members, worked on an adaptation of project due to the evolving nature of the COVID-19 pandemic. So EBA put together an **Amendment** with the approval of the Advisory Board, to extend the duration of the project by 12 months. As a result of this extension, WP7 will continue to support WP2 and WP5 members (that are working on the COVIC-19 clinical trial and on the new updated recommendations) so they can complete their objectives by the new end of the project.

EBA has managed the project's **financial**, **administrative** and **contractual activities** concerning the fulfilment of all obligations within the project in compliance with the general conditions and provisions set forth within the Grant Agreement. To date EBA is successfully administering the financial resources of the project, complying with the rules and procedures set out by the European Commission including ensuring all payments are received and promptly transferred to Consortium members.

Throughout the upcoming months, EBA will continue the strategy used in the first and second reporting period and will assure the final round of funding will be transferred to all partners accordingly.

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Partners

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Aarhus University Hospital

Sistema Socio Sanitario
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