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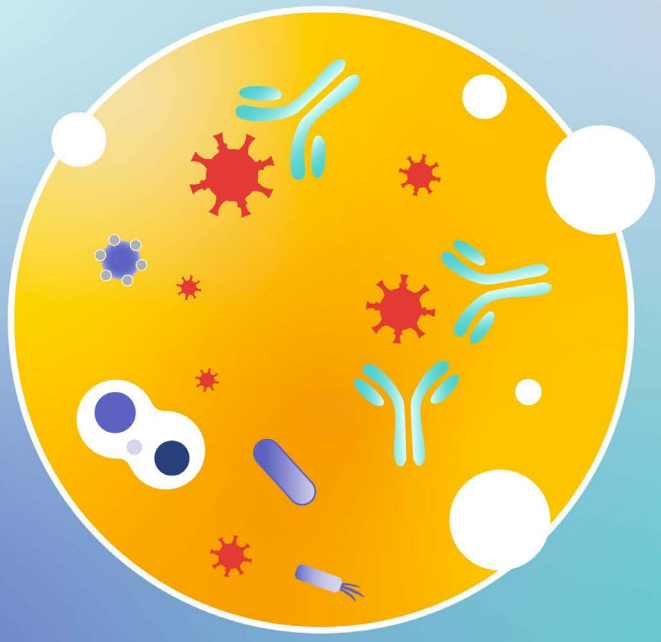
SUPPORTing high quality evaluation of covid-19 convalescent plasma throughout EUROPE

www.support-e.eu

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)

The main goal of the SUPPORT-E project is to provide support to high quality clinical evaluation of **COVID-19 Convalescent Plasma (CCP)**. 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.

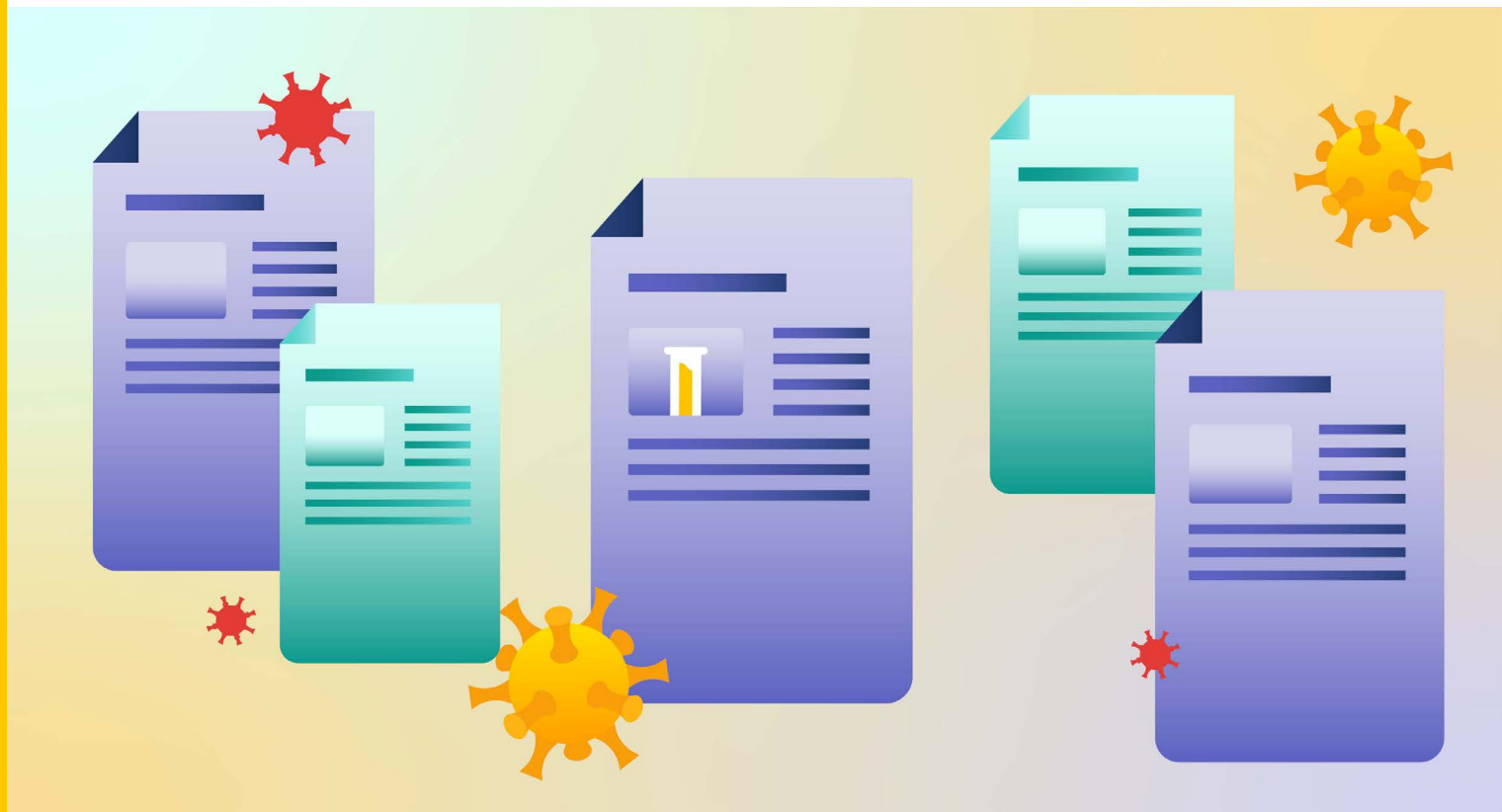
The team is represented by **SUPPORT-E Consortium** that is composed of 12 partners under the leadership of the European Blood Alliance, the association of not-for-profit Blood Establishments (BEs), with 26 members throughout the European Union and EFTA States that overall manage 17 million blood donations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

About CCP

CCP is plasma collected from COVID-19 recovered patients. CCP contains antibodies that could neutralise SARS-CoV-2 and thus may improve disease course in patients with SARS-CoV-2.

About EU-CCP Database

The European Commission is working together with Member States, the European Blood Alliance (EBA) and the SUPPORT-E project partners to provide a platform to support the study of convalescent plasma as a treatment option for COVID-19 patients. The open-access database gathers and makes available data on CCP donations and patient outcomes following transfusions. It includes data from European blood establishments regarding convalescent donors, plasma collection, and plasma components, as well as from clinical trials and from wider monitored use and will consolidate European evidence on the safety and effectiveness of this therapy.



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 test used to quantify the titer of neutralising antibody for a virus.

Microneutralisation (MN) assay
A highly sensitive and specific test for detecting virus- specific neutralising antibodies.

Enzyme-Linked ImmunoSorbent Assay (ELISA)
A plate-based assay technique designed for detecting and quantifying soluble substances such as peptides, proteins, antibodies, and hormones.

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 MANAGE AND COORDINATE PROJECT AND PROJECT FINANCES

WP 6 DISSEMINATE PROJECT RESULTS

WP 1

ASSESS AND MONITOR THE ONGOING AND UPCOMING CLINICAL TRIALS

- Produce preliminary clinical trials guidelines and assessment criteria.
- Produce preliminary monitored access programmes guidelines.

WP 2

INCLUDE SELECTED CLINICAL TRIALS AND MONITORED ACCESS PROGRAMMES IN SUPPORT-E AND PROVIDE FUNDINGS

- Elaborate a new kind of clinical trials to evaluate CCP.
- Ensure high quality data set accrual in EU CCP Database.
- Contact stakeholders to promote the new generation clinical trials.

WP 3

MANAGE THE EU CCP DATABASE AND COLLECT THE DATA

WP 2 - 3

Analyse data collected in EU CCP Database.

WP 4

MAP THE USE OF ANTIBODY ASSAYS FOR THE CCP DONORS SELECTION

- Provide access to neutralisation assays.
- Develop, calibrate and standardise novel neutralisation assays.
- Establish a connection between antibody characteristics and clinical outcomes.

- Perform SWOT assessment to support future SoHO development.
- Create a mathematical model that will assist EU countries to financially manage the activities that are required to provide CCP as therapy during future pandemics.

WP 5

INTEGRATE ALL THE INFORMATION GENERATED BY THE PROJECT

- Formulate recommendations on therapeutical use of CCP.

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

The main and initial objective of WP1 was to assess the current state of the art regarding the collection, characterization and efficacy of CCP in the treatment of patients with COVID-19 through by analysing published and ongoing studies. To achieve this objective, a broad electronic literature and guidelines search was performed in the major online databases to identify both studies on the use of CCP in COVID-19 patients and best practices in monitored access use. For this task 2,855 articles, 2,944 clinical trials and 3,018 monitored access studies were reviewed. After the analysis of the contents only 22 articles, 363 clinical trials and 319 monitored access studies were considered relevant. Following the initial screening, the main characteristics of the various protocols of clinical trials and monitored access programmes were collected highlighting the common and different aspects between the European protocols and then between European and non-European protocols. The WP1 team was able to produce the criteria for high quality evaluation and selection of clinical trials and monitored access programmes based on this relevant literature screening. The screening process will continue until the end of the project and developed criteria will be adjusted if necessary.

Reviewed so far:

- **2,855 articles**
  - 22 considered relevant
- **2,944 clinical studies**
  - 363 considered relevant
- **3,018 monitored access studies**
  - 319 considered relevant

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

Based on the selection of eligible clinical trials and monitored access programmes by WP1, and a Guidance (developed jointly by WP1 and WP2), WP2 aimed at including selected trials and monitored access programmes into the project, eventually providing fundings for those trials and/or programmes with limited own resources. In the early stages of the project, 18 randomised and 9 non-randomised trials or programmes were contacted by WP2 team, 17 of them expressed interest in participating. Among these, , 9 randomised and 4 non-randomised trials or programmes were contacted in the second phase and 4 of them expressed interest to join the project. An extended analysis of the design of the trials selected so far for inclusion in SUPPORT-E has then been performed. Based on the outcome of this gap analysis, the SUPPORT-E Consortium decided to develop and initiate the design of a "next generation" clinical trial the so-called "COVIC-19" (Randomized Open-Label Trial of Convalescent Plasma Therapy in Clinically Vulnerable Individuals with Mild COVID-19). This randomized phase III clinical trial combines several features to an innovative optimized treatment approach, which distinguishes this COVIC-19 trial from other CCP trials and includes:

1. Immunotherapy with plasma containing high concentrations of neutralizing SARS-CoV-2 antibodies obtained through a combination of natural SARS-CoV-2 infection and an immunological boost by SARS-CoV-2 vaccination.

2. Administration of the CCP from recovered, vaccinated donors very early after onset of symptoms in acute SARS-CoV-2 infection (within 5 to 7 days).

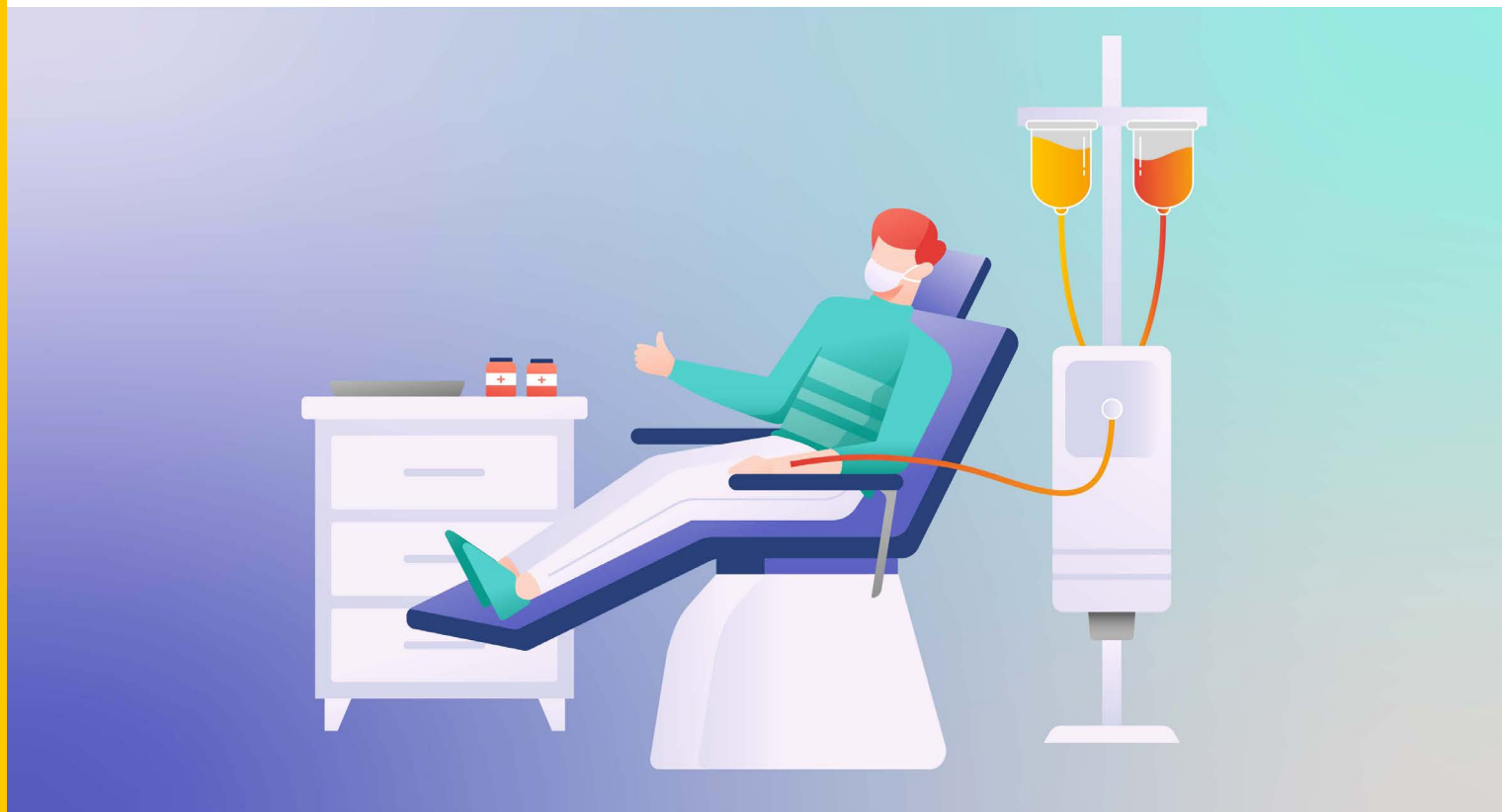
3. Treatment of patients in need, i.e., vulnerable patients who are at high risk of progression to severe COVID-19, notably patients with underlying immunodeficiency.

4. Analysis of SARS-CoV-2 strains in the patient population to study potential implications of viral evolution and immune escape on antibody-based therapy.

A detailed clinical trial protocol for COVID-19 has been developed and has been submitted for regulatory approval. The COVID-19 trial will be conducted in Germany, France, United Kingdom, and Netherlands. The trial has started in Germany with over 50 patients included by September 1st 2022.

Highlight:

- An **extended gap analysis** of the design of selected trials has been performed.
- Based on this, the **design of a "next generation" clinical trial** addressing these critical knowledge gaps was developed and already started in Germany.



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 will be managed jointly by EBA and the European Commission. The Activities within this work package focus 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. At the end of June 2021, a little more than 1 year after opening the database, more than 137,000 recorded plasma donations of COVID-19 convalescent donor from over 55 European BEs were recorded. The database also made it possible to collect data related to 823 patients (from 8 contributing countries), who had received CCP during their treatment. The consortium is aware that this figure is rather an underestimation and does not represent the real situation of the use of CCP in the treatment of COVID-19. 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.

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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.

Recorded so far:

- **137,000 CCP donations** from over **55 European blood enstablishments**.
- Data related to **823 patients**, from **8 contributing countries**.

WP 4 – Improving plasma potency assessment

The early stages of WP4 teamwork focused on establishing an inventory regarding access to and nature of SARS-CoV-2 antibody testing. The team created an online survey to map the use of antibody assays for the selection of CCP across EU member states. The questionnaire was distributed to 46 involved physicians (26 from EBA associated BEs, 20 principal investigators of new and ongoing CCP clinical trials across the EU) and 29 responses were collected. The most important observation in responses analysis was a huge heterogeneity in strategy to select CCP donors and the type of assay used to test plasma/serum of CCP donors to select for high antibody titres. In order to standardize CCP testing across Europe and carry out the calibration of IgG levels to an international standard, a panel of 23 convalescent plasma samples has been constructed containing a mixture of SARS-CoV-2 antibody negative, low, medium, and high-titre positive samples. This panel of characterized CCP samples serves as internal standard for all antibody assays, making results comparable and has been shared with 25 labs of collaborating members to test them for the presence of neutralising antibodies according to their normal procedure. 16 labs have returned results earlier than expected with very enthusiastic responses, the others were contacted individually and supported. A total of 100 samples from laboratories that needed assistance were tested with a live virus and pseudovirus neutralisation assays, and results will be incorporated to the database.

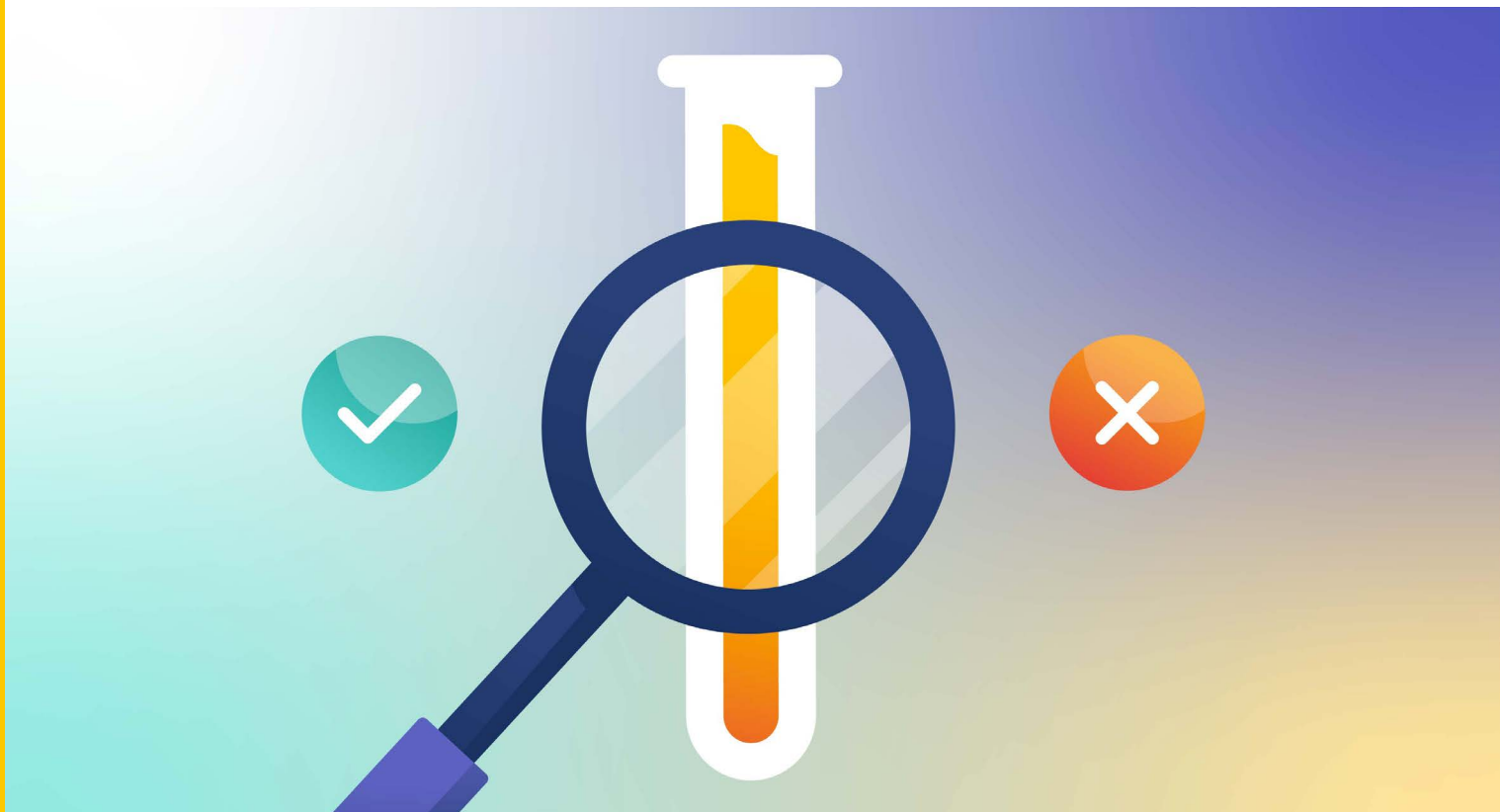
Since the virus mutated and the relevance of such variants was soon established, live virus microneutralisation assay and pseudovirus neutralisation assays have been regularly updated (through the introduction of the main variants to the virus at the time: Alpha, Beta and Delta) into routine use within WP4 at the University of Oxford, in order to constantly support any SUPPORT-E participants if/when needed.

WP4 Team also compared commercial ELISA-based assays used for donor selection with plaque reduction neutralization test (PRNT) or microneutralization (MN) assays. This analysis, that resulted in many peer-reviewed publications, suggested that some commercial ELISA assays may perform effectively as surrogate assays or serve as a reliable proxy for neutralizing antibody titre. Not all assays perform equally well, so a specific assay may be preferred but such assays are more rapid than live virus tests and appear more reproducible in general.

Highlight:

- To standardize antibody testing in CCP a panel of **23 convalescent plasma samples has been constructed** containing a mixture of negative, low, medium, and high neutralization titre positive samples and was **shared with 25 labs**.

- Also, the **comparison between results of commercial ELISA-based assays** used for donor selection and plaque reduction neutralization tests (PRNT) or microneutralization (MN) assays showed that ELISA assays may perform effectively as surrogate assays or serve as a **reliable proxy for determining the neutralizing antibody titre in CCP**.



WP 5 – Developing recommendations and preparing for the future

To determine the safety and relative effectiveness of CCP, the WP5 team examined all the studies that compared CCP to placebo or standard of care for COVID-19 patients and all the studies that compared CCP treatment to standard plasma. The review identified the three main limitations of all the available data.

1. Due to the rapid and unforeseen severity of the COVID-19 pandemic there was insufficient time to develop a reliable standardised method to measure the dose of antibodies in the CCP units used.

2. Differences in the volume of CCP given will also influence the dose of anti-SARS-CoV-2 activity for each patient.

3. COVID-19 has varied presentations of the onset of disease and the understanding of how these develop and how they are related to disease pathology is continually evolving.

WP5 team has also begun to develop a mathematical model that will assist EU countries to financially manage the activities that are required to provide CCP as therapy during future pandemics. The Health Economics Research Centre (HERC), University of Oxford, used budget impact analysis of CCP programmes. HERC has compared two scenarios, the financial impacts in a world with CCP and a world without CCP, to assess the affordability of a CCP programme and provide information for national-level decisions makers for planning purposes. Key aspects to consider in analyses were the eligible population for CCP donation and current care for this population, the uptake of CCP, the cost of the national programme and the direct impact of CCP on healthcare resource use and costs.

A SWOT (Strengths, weaknesses, opportunities, threats) assessment is also in early stages of development. An initial list of SWOT include:

1. Strategies to recruit donors of CCP to target new variants of disease. To include findings in WP1 and WP4.

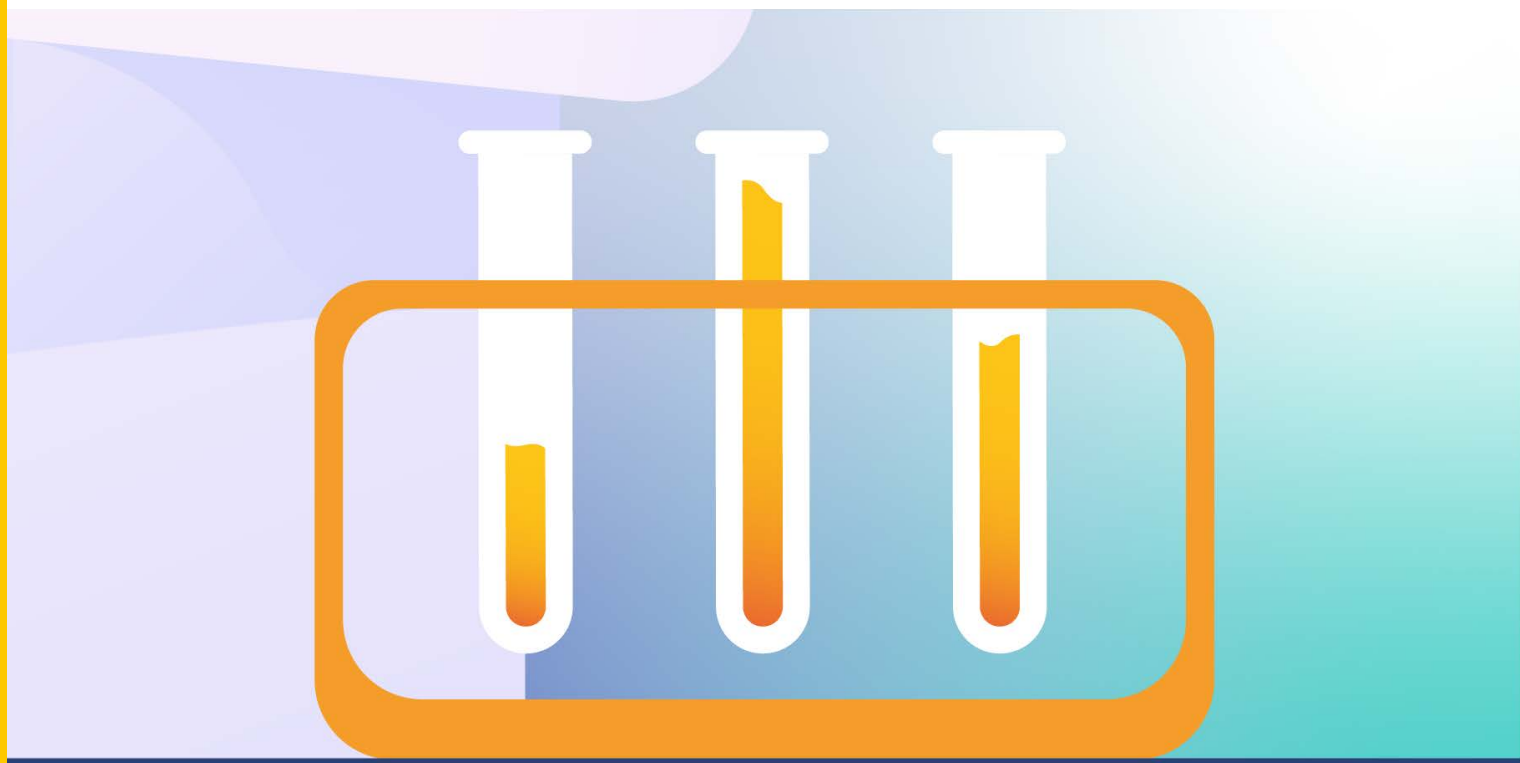
2. Database for CCP collected during different waves of the pandemic to correspond with emergence of new variants. To include findings in WP2 and WP3.

3. Training site and resources for measurement of neutralising antibody titres to ensure agreement in dose of CCP used across different nations using standardised methods. To include findings in WP4.

4. Distribution service(s) to support quick and efficient use of CCP across network of countries.

Highlight:

WP5 team has begun to **develop a mathematical model** that will assist EU countries to financially manage the activities that are required to provide convalescent plasma as passive immunotherapy during future pandemics.



WP 6 – Dissemination, exploitation and communication

A dissemination, exploitation and communication strategy was drawn up by the team leader, Centro Nazionale Sangue-Istituto Superiore di Sanità. The strategy was created to enable a structured approach to be taken by all project members for SUPPORT-E dissemination activities. The chosen strategy emphasizes the responsibility of every partner to contribute on the dissemination share all the material produced with relevant target groups. Such relevant target groups were defined in relation with the topics of the technical work-packages and classified under three main categories:

1. Institutional level (international/European and national competent authorities, policy makers and organizations).

2. Professional level (national and international professional societies e.g. in the fields of transfusion medicine, haematology, apheresis, internal medicine, intensive care, etc.).

3. Final users (healthcare providers, donors and patients).

As for the dissemination material, a collaboration was established with a communication agency, specialised in brand identity, web content design and 2D and 3D animated video production. Specifically, the project visual identity was established through the creation of 2 logos and website layouts proposals, which were shared for partners' selection and approval. The SUPPORT-E website (https://www.support-e.eu) was successfully launched as well as a Twitter account. In addition, Word and PowerPoint template were created, including a formal headed paper. A newsletter, 2 press releases, a promotional video and the first series of mini-interviews entitled "A brief talk with SUPPORT-E Team" were launched to reach out generic audience and specific targets.

The WP6 Team reached out to several EU parallel projects exploring potential collaboration considering the common goals that are mainly

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long-term understanding of the disease and development of therapies for COVID-19 and future threats as well as patients care and protection. In particular, contacts have been made and introductory calls were organised with RECODID, MANCO, CoroNAb, ATAC, CARE. This team outreaching efforts focused on sharing objectives and actions of the respective initiatives.

Scan the QR codes to access the newsletters, mini-interviews and promotional video:

▶ WEBSITE

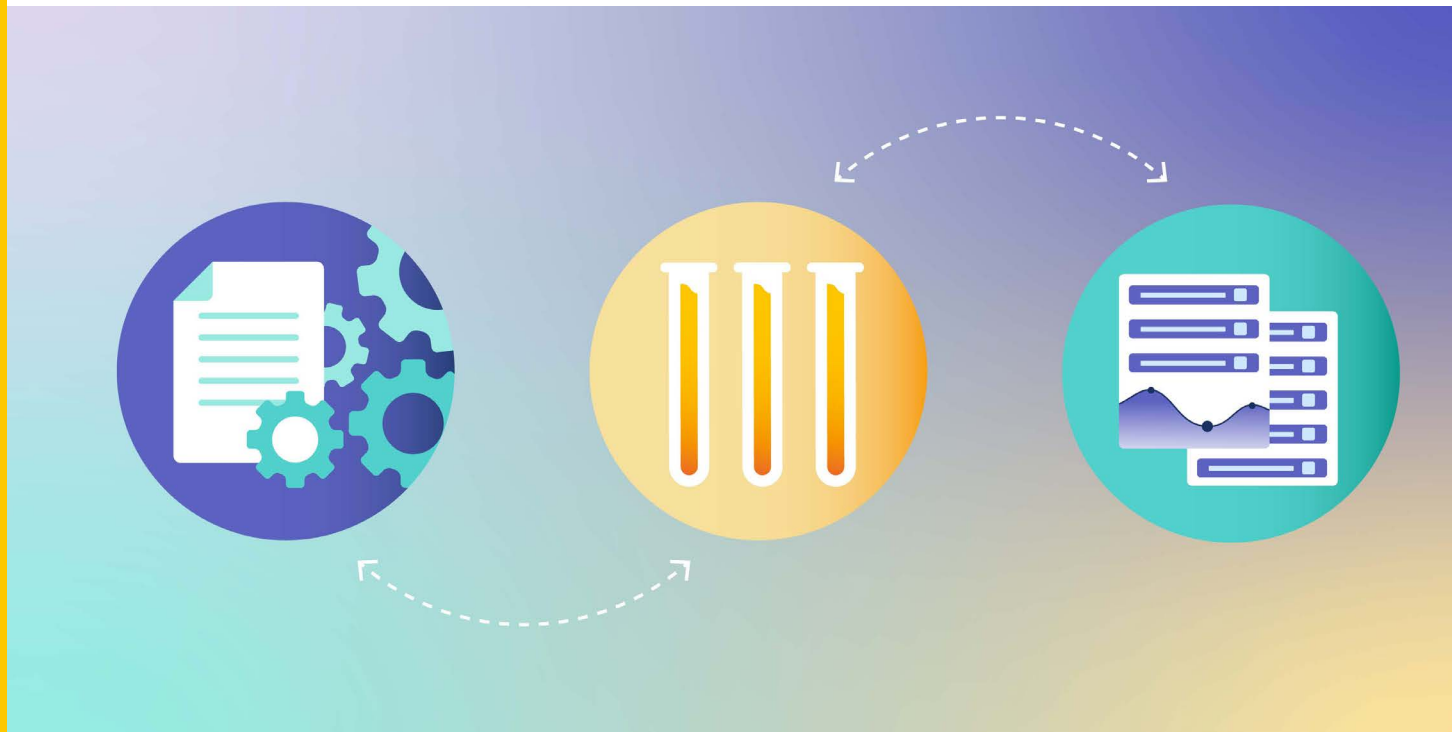
▶ VIDEO

WP 7 – Project management

WP7 team ensured that project implementation by the partners was compliant with the conditions set forth in the Grant agreement and the Consortium agreement. To achieve this objective, monthly meetings with all Consortium members and quarterly meetings with the SUPPORT-E Ethical and Scientific Advisory Board were organized. The coordinators have liaised with each WP through regular meetings to coordinate the timely delivery of each WP Deliverable as well as coordinating the collaboration within WP and external members. These include regular progress reports for both external and internal stakeholders. The coordinators are also leading the registration of Blood Establishments on the EU CCP Database and take part in regular calls in relation to this. Regular contact is kept with the European Commission on the status of the project.

WP7 team has also acted as an intermediary for all communications between the beneficiaries and the European Commission. To this end team leader EBA had regular communications with all actors and kept a detailed eye on the progress and the overview of tasks to be carried out to support all the partners and provide clarity on the responsibilities and procedures.

EBA also 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.



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