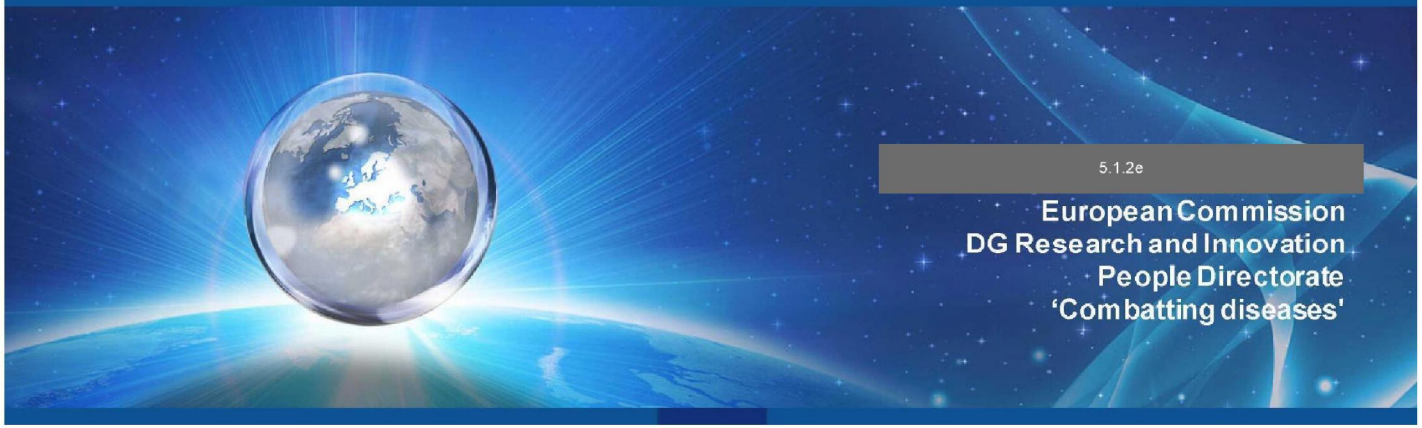
The European research triggered by the COVID pandemic: the convalescent plasma domain



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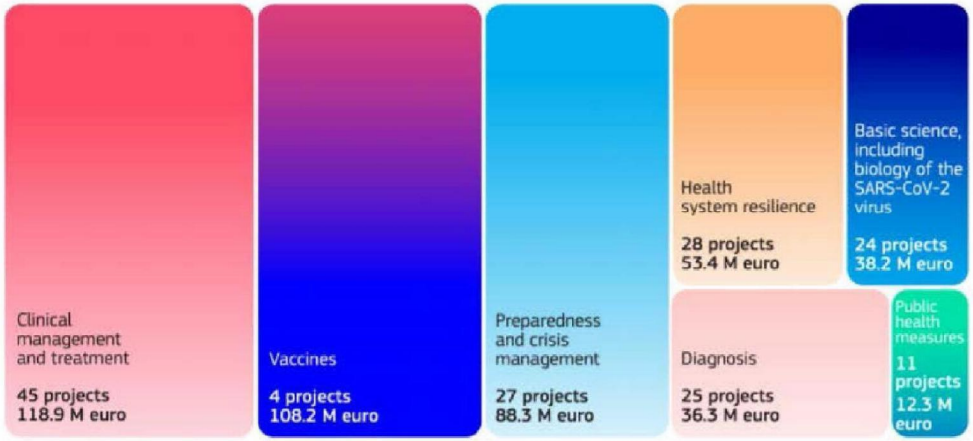
Horizon 2020 R&I against coronavirus

1. EU funding to combat COVID-19: focus on treatment, vaccines and crisis management

FIGURE 1: DISTRIBUTION OF COVID-19 H2020 PROJECTS ACCORDING TO MAJOR NEEDS BY ESTIMATED EU FINANCIAL CONTRIBUTION (M EURO)



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469m€ for 105 COVID-related research projects

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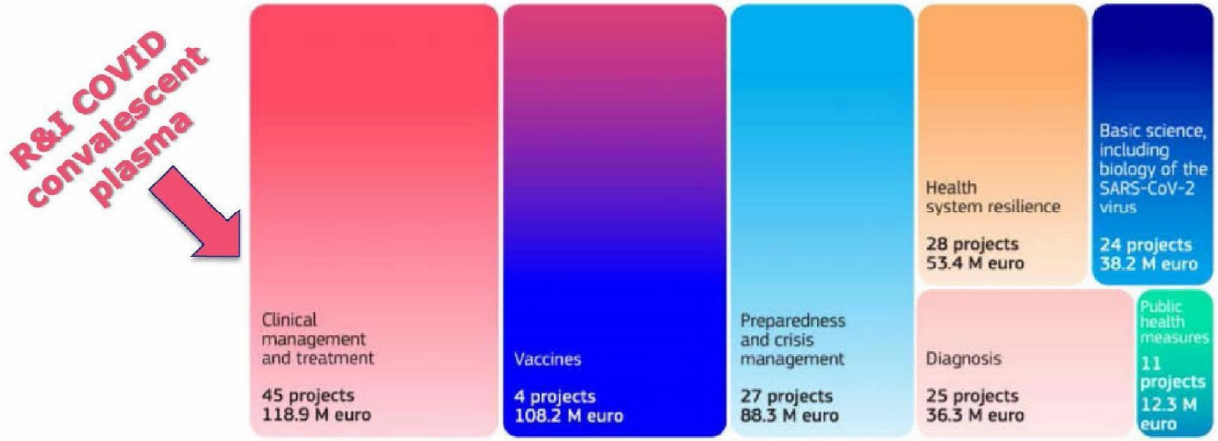

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Support-e

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

www.support-e.eu

info@support-e.eu

SUPporting high quality evaluation of COVID-19 convalescent Plasma thrOughoutT Europe

H2020 EU contribution €4 million

Coordination: European Blood Alliance (EBA)

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12 participants (from The Netherlands, Germany, Italy, Belgium, Denmark, UK, Switzerland)

Start date: 1 July 2020 (duration 2y)

- **Assessing** CCP, conducting clinical evaluation and defining best practises.
- **Supporting** high quality clinical evaluation and producing datasets for inclusion and analysis in the EU-CCP database. Facilitating anti-SARS-CoV-2 antibody testing and establishing the relationship between antibody (Ab) content in donor plasma and clinical outcome.
- **Developing harmonised recommendations** on CCP collection, testing and therapeutic use to treat Covid-19 and paving the way to prepare for future epidemics/pandemics with novel pathogens across the EU.

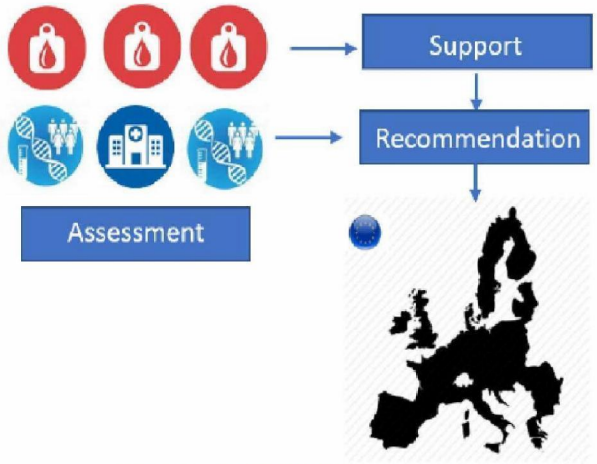

Figure 1-1 - The SUPPORT-E project concept

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

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Achievements

01 Support high quality clinical evaluation of CCP throughout the EU

provides specific support to clinical trials and monitored access programmes, based on carried-out review and Guidance documents on assessment criteria. Up to now: 13 randomised and 9 non-randomised clinical trials have been selected.

02 EU-CCP Database

Open-access EU CCP database: gathers and makes available data on convalescent plasma donations and patient outcomes following transfusions. SUPPORT-E is promoting high-quality data sets in the EU CCP database by providing financial support for data submitted.

03 Assay calibration

Variability between tests across Europe has been mapped (questionnaire) on access to and nature of antibody testing and virus neutralization testing. Results: majority of respondents (20) did not have access (in house or outsourced) to live-virus or pseudotype neutralization testing. Only 9 reporting access.

04 Health Economics of COVID-19 plasma

In collaboration with Oxford University (Health Economics Research Centre), a consultation was carried out to evaluate the costs and benefits associated with CCP collection and testing using different strategies.

05 Opinion paper published in Vox Sanguinis

Evaluation of SARS-CoV-2 antibody titers and potency for convalescent plasma donation (*Wouters et al*).
The paper describes the major issue(s) with testing of CCP for antibodies against SARS-CoV-2.
https://onlinelibrary.wiley.com/doi/10.1111/vox.13060

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In the pipeline..

01 COVIC-19 trial proposal

A Randomized Open-Label Trial of Convalescent Plasma Therapy in Clinically Vulnerable Individuals with Mild COVID-19 (COVIC-19).
COVIC-19 addresses some of the knowledge gaps identified

02 CCP neutralisation of variants / variants sequencing

Investigation for a potential collaborative work: SUPPORT-E to provide laboratory capacity to the emergence and spread of SARS-CoV-2 variants in Europe (to assess their potential effect to convalescent plasma efficacy).

03 Assay calibration

support to calibration and cross border standardization of assays in EU Member States (via distributing standards to the Blood Establishments identified in questionnaire and analyzing that data)

04 Developing recommendations and preparing for the future

SWOT analysis in terms of CCP collection, testing and use during the first wave of the COVID-19 crisis

05 SUPPORT of monitored access use programmes

With support of CA and clinicians, monitored access programmes will be contacted to assess the inclusion of monitored access use programmes in SUPPORT-E (operational aspects and financial support).

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AYAC

https://covidantibodytherapy.info/

Antibody Therapy Against Coronavirus (COVID-19)

H2020 - EU contribution €3 million
Coordination: Karolinska University (KI) 5.1.2e
5 participants (Sweden, Germany, Italy, Belgium, Switzerland)
Start date: 1 March 2020 (duration 2y)

Preclinical development of antibodies against SARS-CoV-2

ATAC uses a novel approach to immunotherapy development against COVID-19 by leveraging three different and independent methods:

- gamma-globulin immunotherapy (KI)
- Generation and selection human antibodies in the laboratory by library screening (Technische Universität Braunschweig (Germany)
- Selection of antibodies from convalescent plasma and *in vitro* optimisation to generate recombinant monoclonal antibodies (Institute of Research in Biomedicine (IRB)

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Antibody therapy against coronavirus (ATAC)

Planned work

- To generate purified hyperimmune gammaglobulin batches from convalescent COVID-19 patients
- To evaluate the resulting gammaglobulin preparation for virus neutralization *in vitro*
- To test gammaglobulin in critically ill patients (compassionate use)

Work performed

- **Follow the immune response in plasma of recovered individuals in Italy and Sweden**
  - Collect plasma from convalescent donors (mild to severe)
  - Follow IgM, IgG and IgA antibodies anti-RBD and anti-S-protein for a period of 6-8 months
  - Follow the neutralization activity against SARS-CoV-2 virus
  - Sherina *et al.* Med (in press)

- **Hyperimmune plasma therapy for treatment of critically ill patients in Italy**
  - Collect plasma from convalescent donors
  - Treatment of moderate to severe COVID-19 patients treated with hyperimmune plasma
  - Perotti *et al.* 2020. Haematologica 105:2834-2840

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Proof-of-concept study - hyperimmune plasma therapy

- One arm, multicenter interventional study on a short term (7 days) on 46 severe COVID patients.
  - March 25-April 28 (NCT04321421)
- Two university hospitals and one general hospital in Northern Italy
  - Fondazione IRCCS, Policlinico San Matteo

Conclusions:

- Benefit of hyperimmune plasma in COVID-19 patients, both through a reduction of mortality, an improvement in respiratory function and decreases in inflammatory indices.
- Need to be confirmed in a larger randomized controlled trial

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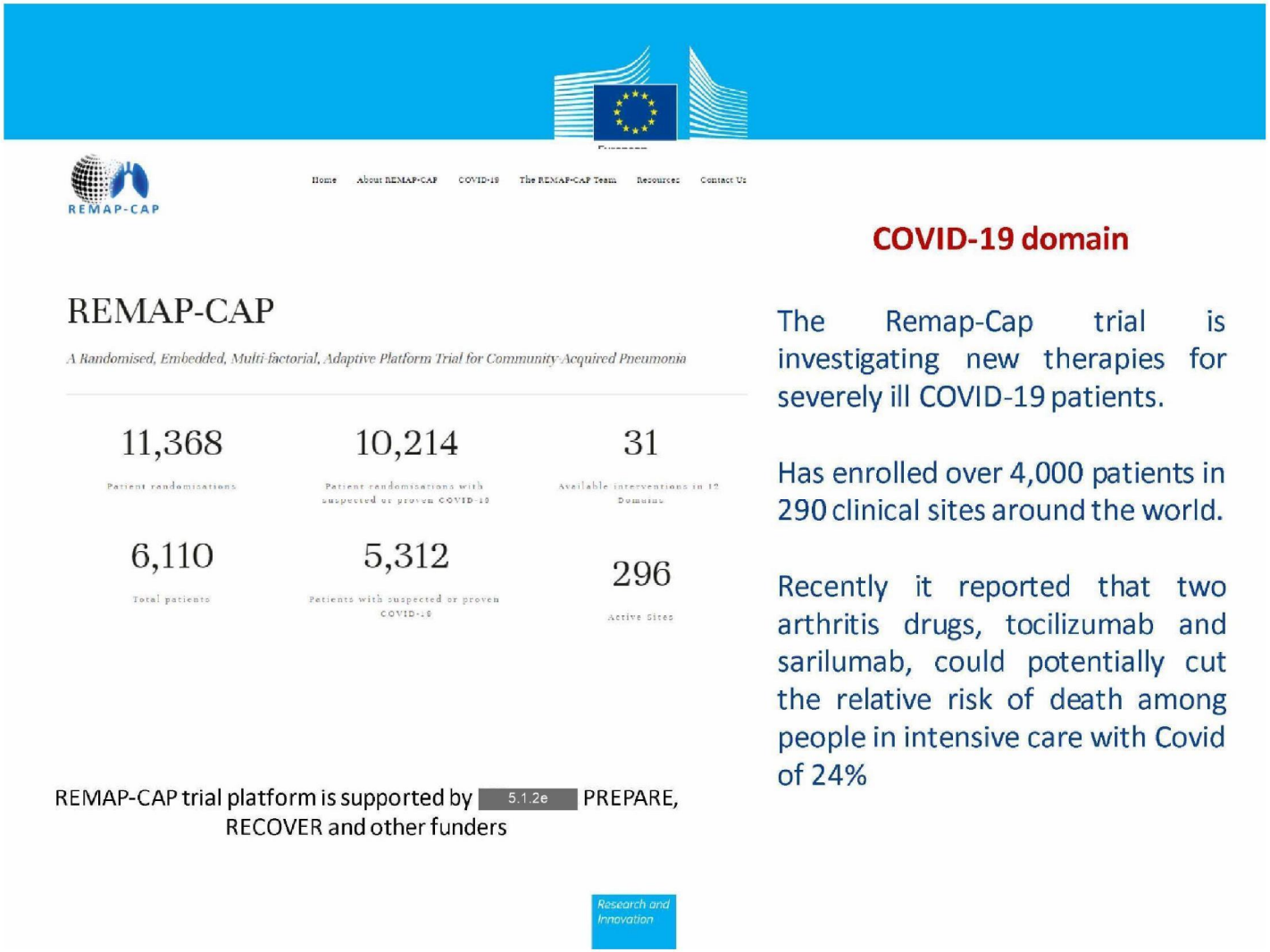
Perotti *et al*. 2020. Haematologica 105:2834-2840



COVID-19 domain

The Remap-Cap trial is investigating new therapies for severely ill COVID-19 patients.

Has enrolled over 4,000 patients in 290 clinical sites around the world.

Recently it reported that two arthritis drugs, tocilizumab and sarilumab, could potentially cut the relative risk of death among people in intensive care with Covid of 24%

REMAP-CAP

COVID-19 Domains

All participating sites will be able to participate in two existing domains that have relevance to the treatment of patients with severe CAP resulting from coronavirus. These are:

- Evaluation of prolonged macrolide therapy, as a modulator of immune function
- Evaluation of alternative corticosteroid strategies (no corticosteroids, low dose hydrocortisone for 7 days, or hydrocortisone while the patient is in septic shock)
- Evaluation of no antiviral therapy for COVID-19 (and no placebo), lopinavir/ritonavir (Kaletra), hydroxychloroquine, and the combination of hydroxychloroquine and lopinavir/ritonavir
- Evaluation of no immune-modulating therapy for COVID-19 (and no placebo), Interferon-beta-1a, interleukin-1 receptor antagonist (Anakinra), tocilizumab and sarilumab.
- Evaluation of the use of convalescent plasma for COVID-19

NHSBT responsible trial management

- Evaluating therapeutic dose anticoagulation using low molecular-weight heparin or unfractionated heparin compared to standard pharmacologic thromboprophylaxis
- Evaluation the use of high-dose vitamin C for patients with severe CAP including CAP caused by COVID-19
- Evaluation of the use of simvastatin for COVID-19
- Evaluation of the use of aspirin or a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) compared to no antiplatelet therapy
- Evaluation of angiotensin converting enzyme inhibitor (ACEi), angiotensin-II receptor blocker (ARB), an ARB in combination with a chemokine receptor-2 inhibitor, or no renin-angiotensin system inhibitor for patients with COVID-19

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REMAP-CAP

Current status:

In January, REMAP-CAP trial **halted recruitment** to its convalescent plasma arm on the recommendation of the data safety monitoring board. An **interim analysis** that was based on data from **912 patients** found that the probability that convalescent plasma was beneficial was 2.2% (no benefit).

Analysis is still ongoing to assess whether plasma could benefit subgroups of patients (e.g. those with low natural antibody levels).

Some other international trials are also testing plasma effect when used very early in the disease, before people are hospitalized (already some evidence available). Similar trials are discussed in the UK and other EU countries.

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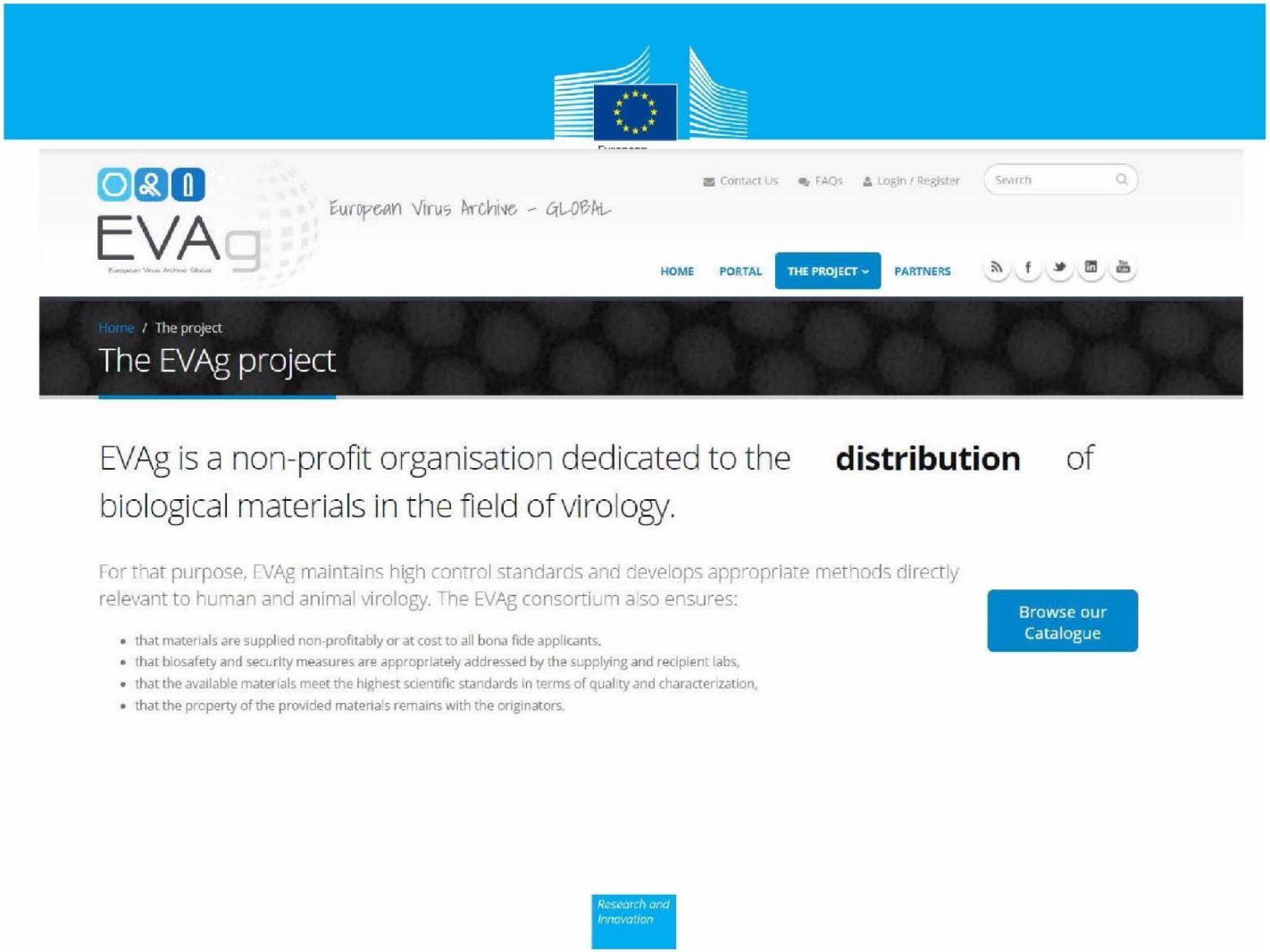
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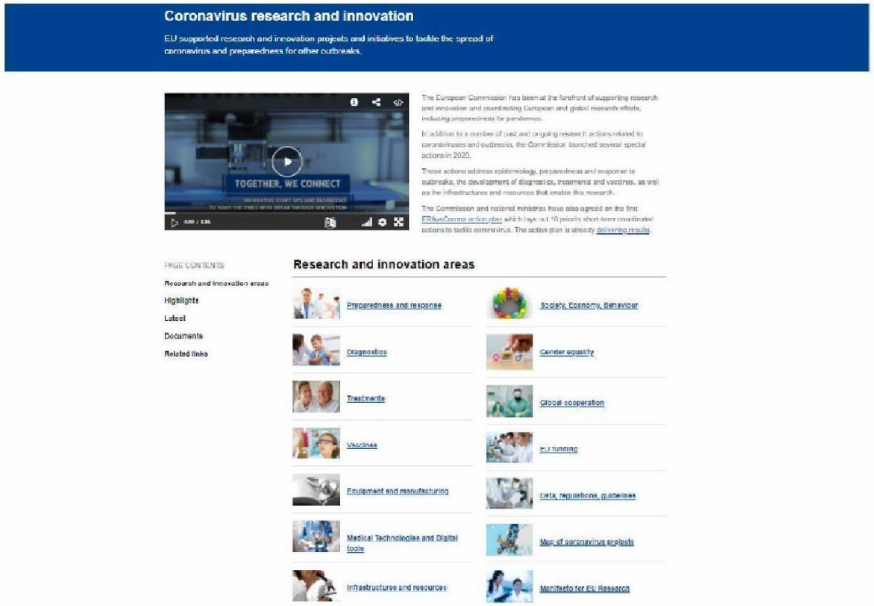

https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/coronavirus-research-and-innovation_en

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