

From Crisis to Innovation: How the CARE Consortium has Shaped the Future of Pandemic Response

CARE White Paper

CARE Executive and Steering Committees

On behalf of Corona Accelerated R&D in Europe (CARE), consortium members reflect on the unique features of this large collaborative research effort that contributed to CARE's progress in finding new therapies against SARS-CoV-2 and potential future coronavirus outbreaks.

Summary

The Corona Accelerated R&D in Europe (CARE) consortium was formed in April 2020 in response to the urgent need for solutions to combat SARS-CoV-2. Comprised of 38 organisations from Europe, the USA, and China, CARE focused on drug repurposing, new small molecule drug discovery, and discovery of virus-neutralizing antibodies which would be useful for both current and future coronavirus outbreaks. With a EUR 75.8 million grant, the consortium has made significant contributions to the fight against COVID-19, including developing novel drug candidates and expanding research tools. As the project approaches its conclusion in March 2025, the CARE consortium reflects on its accomplishments and the ongoing relevance of its work, especially considering ongoing threats from viruses with pandemic potential.



Foreword from the CARE Scientific and Ethics Advisory Board

CARE has made significant progress towards its goal to develop new drugs to fight COVID-19 and future pandemics, not only through small molecule and antibody compound discovery and innovation, but also through the evaluation of compounds from outside the consortium as a promising alternative strategy. CARE's unique collaborations, insights and technologies for COVID-19 have had international scientific impact; importantly, the consortium is a model for accelerating pandemic response and preparedness. Academia has many innovative ideas that can result in impactful products if paired with reputable drug discovery centres and industry partners who understand quality, reproducibility and commercialisation. We have seen measurable growth of CARE with increasing productivity and cross fertilisation across work packages, that has blossomed over time.

When it was originally funded, addressing the COVID-19 global pandemic had a clear imperative. Though the pandemic has receded, new variants of the virus are constantly emerging, and individuals, particularly the immunocompromised, continue to suffer morbidity and mortality. The achievements of the CARE consortium therefore remain highly relevant.

Despite not being able to realise its objective to reach the clinical trials stage, CARE has made significant advances in both scientific and operational understanding for pandemic response efforts on a number of fronts.

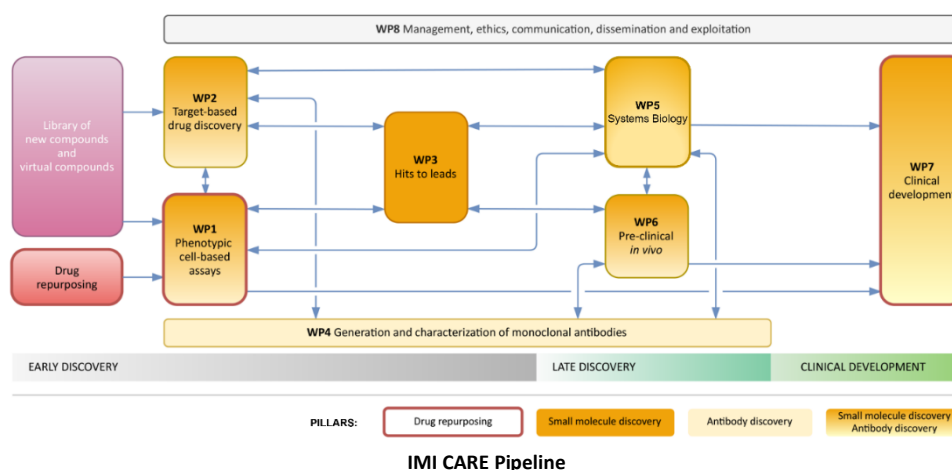
Introduction

The emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in late 2019 and the subsequent COVID-19 pandemic posed unique challenges to the research community¹. It meant the global scientific community needed to develop new therapies at an unprecedented pace. ([The race for antiviral drugs to beat COVID — and the next pandemic](#)). However, having to address a new virus from a viral family that received too little attention in the past decades, with limited available knowledge, especially regarding assays or research tools, posed significant challenges. This called for an innovative strategy providing the breadth of expertise, resources and agility necessary to develop effective treatments at speed against a rapidly mutating target. ([Funders, now is the time to invest big in COVID drugs](#)).

The Corona Accelerated R&D in Europe (CARE) consortium was established in April 2020 to provide an emergency response against SARS-CoV-2 by drug repurposing as well as by discovering, investigating, and developing new small molecules and virus-neutralising antibodies for treatment and/or prevention of both current and novel coronavirus variants of potential importance for future coronavirus outbreaks. CARE brought together 38 academic institutions, research organisations, small biotech and large pharmaceutical companies from across Europe, plus partners from the USA and China, who are leaders in their areas of expertise (www.imi-care.eu). The rapid provision and size of its funding, with more than 75 million Euros – half provided by the European Union Innovative Medicines Initiative and half by the European Federation of Pharmaceutical Industry Associations and Associated Partners – just a few weeks after its call for research proposals in early 2020 (Call details: [IMI2 - Call 21](#), Grant agreement number 101005077), put the consortium in a strong position to hit the ground running and spearhead SARS-CoV-2 research efforts.

A multidisciplinary approach

Typically, we describe drug discovery as a linear process which can be siloed by stage, for example, from screening, hit-to-lead, lead optimisation, pre-clinical proof of concept and first in human studies. In the CARE consortium, capacity for each stage of the development process was established in parallel and siloes were broken between the stages through sharing of capability and the establishment of multidisciplinary steering and working groups. This enabled rapid, focused progression of promising molecules and facilitated innovation through iterative learning. All parties have worked in research collaborations previously, but never with such breadth of experience. This multidisciplinary approach enabled tackling scientific challenges out of reach of individual research groups working on their own. The five-year project allowed sharing of knowledge and assets, including compound libraries and assays, to identify promising drug candidates and develop them into new treatments. The CARE project comprised three pillars and eight work packages:



The COVID-19 emergency response pillar focused on drug repurposing, screening drug or clinical compound libraries contributed by partners. The small molecule discovery pillar focused on phenotypic and target-based screening against SARS-CoV-2 to identify hits which were then optimised by the medicinal chemistry work package. The third pillar focused on the discovery of virus-neutralizing antibodies using platforms that included, but were not limited to, isolation of B cells from COVID-19 patients and immunisation of fully human IgG transgenic animals. The systems biology work package investigated virus-host interactions and identified immune markers of disease progression. In addition, preclinical and clinical work packages delivered platforms for evaluating therapeutic candidates, as well as generating patient evidence and regulatory guidance for potential market access. All the pillars and work-packages continuously adapted based on the evolution of SARS-CoV-2.

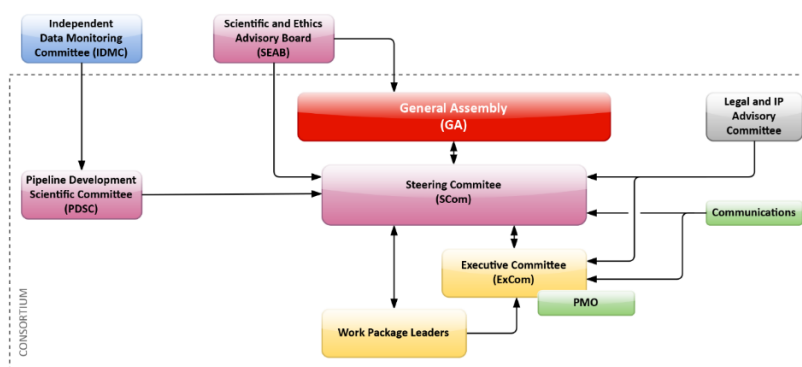
Tapping into world-class expertise

Academic partners, including reputable drug discovery centres, contributed fundamental expertise and technologies for understanding the SARS-CoV-2 virus including capabilities in antiviral drug screening, design and synthesis of compounds, structural analysis of viral proteins, animal model development and clinical trials, as well as the provision of patient evidence related to potential COVID-19 medicines and regulatory insights. This enabled partners who are generating small molecules and antibodies to define and characterise candidate therapeutics quickly and, by understanding their characteristics upfront, enabled more informed decisions on the progression of molecules. Furthermore, the consortium occasionally reached out to external expertise to enhance its capabilities and expedite the achievement of its objectives.

Industry partners brought extensive expertise to the partnership in the design, identification, development, and testing of molecules in addition to the planning and management of the drug development process. This enabled a lean drug discovery and development process, ensuring that priorities were set for lead candidates for the CARE consortium at a very early stage, with drug designers and clinical drug development specialists interacting from the start of our collaborative projects.

Early interaction with the Innovation Task Force (ITF) of the European Medicines Agency (EMA) provided insights into the regulatory expectations for qualification of potential methodologies. In addition, interaction with patients on acceptance of potential COVID-19 medicines informed the development and clinical phases of CARE.

CARE's strong coordination process ensured that this large consortium worked effectively, and learnings could be continuously translated to process improvements. Regular working group meetings within and across work packages encouraged open discussion and brainstorming, while steering committees enabled coordinated decision-making.



IMI CARE Governance

Opening up compound libraries

As a first goal of the project, early in the pandemic, a live SARS-CoV-2 virus-based high-throughput screen (HTS) was set up and validated by KU Leuven² for the discovery and development of hit series. To identify antivirals that could be deployed rapidly in the quickly expanding pandemic, the unique CAPS-IT system of the [Rega Institute of KU Leuven](#) enabled the rapid screening of approximately 20,000 small molecules that had either been clinically validated for other indications before or were selected from the pharma partners' and the [Centre for Drug Design and Discovery \(CD3\)](#)'s compound libraries. Unfortunately, none of the compounds evaluated were deemed suitable to advance towards clinical development.

To further engage in more classic drug discovery approaches, over 1.5 million small molecules were screened in optimised virus-based high-throughput assays³ (phenotypic drug discovery). Assays for validation and triaging of the hits were set up based on activity against emerging variants of concern, other beta coronaviruses (SARS1, MERS, OC43, HKU1), and alpha-, delta- and gamma coronaviruses. Eventually, three novel compound series with activity against SARS-CoV-2 were prioritised for further optimisation towards candidate molecules in the consortium. As validation of this approach, the three series have been shown to act through novel modes of action, opening further avenues for future antiviral drug discovery (see below for more detailed description of the series). This phenotypic approach was an effort across the consortium, including virologists from several groups and medicinal chemists from CD3-CISTIM Leuven, IKTOS, Nuvisan, Takeda, GHDDI, AbbVie and Merck.

To increase the chances of success, this target-agnostic virus-based screening approach was complemented with several target-based approaches. The initial phase of the target-based approach involved the rapid characterisation of key enzymes and macromolecular assemblies that constitute the viral targets. For instance, in the case of the main protease Nsp5, existing knowledge facilitated immediate engagement in the design, synthesis, and testing of compounds, supported by structural data coordinated by the University of Lübeck. However, it was crucial to reconstitute larger multi-assembly complexes to identify more authentic targets in environments suitable for HTS. This was successfully accomplished at Aix-Marseille University with the Replication/Transcription complex, which includes Nsp7/Nsp8/Nsp12⁴ and the Nsp10/Nsp14 complex.

Within this target-based framework, various subsets of chemical libraries, selected through focused screening or large-scale campaigns, have been rigorously tested in close collaboration with corporate partners such as Janssen, MKDG, and Pfizer, alongside the [enzyme-based screening platform at Aix-Marseille University](#). The consortium has made significant strides in inhibiting Nsp14 RNA methyltransferase activity⁵⁻⁹, and exonuclease activity¹⁰ as Nsp14 is a bifunctional enzyme essential for SARS-CoV-2 replication.

Discovery and optimisation of new small molecule antiviral drugs

Following identification of new hit compounds in the phenotypic and target-based approaches, prioritised antiviral hit series were further optimised via thorough medicinal chemistry efforts¹¹.

The first two series were developed in the target-based track. The team from the University of Dundee, in collaboration with scientists from Takeda, the Universities of Leiden, Leuven, Aix-Marseille and Jagiellonian University targeted Nsp14. In a short period of time, they progressed from initial concepts to developing a series of compounds with potent antiviral effects and co-crystal structures¹² and have developed a compound series with potent antiviral effects *in vivo* that could deliver a candidate for further development. This Nsp14 targeting program formed the basis for a license agreement with Novartis. Aside from Nsp14, the team at Al-Biopharma identified and optimised novel nucleoside analogues inhibiting Nsp12. The objective of this latter program was to identify broad-spectrum compounds with a profile differentiated from currently available nucleoside drugs.

Three series coming from the phenotypic-based drug discovery track were prioritised over others, based on target compound profiles established at the start of the consortium. The first series, in advanced lead optimisation led by the team of CD3-CISTIM, shows low nM antiviral activity against all variants of concern of SARS-CoV-2 and against SARS-CoV-1, and yielded strong antiviral efficacy *in vivo*. This series targets the membrane protein, a novel mechanism of action demonstrated after characterising the series via resistance generation, time-of-addition experiments, binding studies and Cryo-EM¹³. The second is a compound series in lead optimisation by Nuvisan, which was identified from the Servier compound library and has yet another mechanism of action. This series seems to act by inhibiting the replication and transcription complex of SARS-CoV-2 (Nsp7/8/12) which was demonstrated by the University of Marseille. This compound series has double-digit nM activity in several cell lines and has already obtained *in vivo* proof of concept. The third series was developed up to a lead stage also yielding *in vivo* proof of concept, but was then deprioritised because of its antiviral properties.

Taken together, the collaborative efforts of all contributing partners along with those of the full CARE consortium have enabled the development of several innovative antiviral compound series which can all further mature to potential candidate antiviral drugs. These efforts serve as a good foundation for the fight against SARS-Cov-2 and potentially future coronavirus pandemics.

Antibody discovery

Understanding the exact region that an antibody is binding to, the contact residues and precisely how it interacts with the viral protein, provides a mechanistic understanding of how an antibody interacts with an epitope in the context of other data on neutralisation, breadth of neutralisation, potency, and cross-reactivity. Typically, research groups don't get this information for this number of molecules at an early stage in programs, but rather when they have reduced to only a few lead molecules, so this early access to expert cryo-EM analysis has enabled earlier informed decisions to be made, accelerating our progress.

Working together, members of the CARE consortium developed a highly potent anti-SARS-CoV-2 antibody, P5C3, which was discovered and characterised at Centre Hospitalier Universitaire Vaudois (CHUV). This monoclonal antibody (mAb) is broadly neutralising, with picomolar neutralizing activity against all SARS-CoV-2 variants of concern identified prior to before the emergence of Omicron variant at the end of 2021 and confers complete prophylactic protection in an animal challenge model¹⁴. The CARE partners developed a second human mAb, P2G3, with picomolar neutralizing activity against Omicron and all other current variants¹⁵. Structural characterisation shows unique binding properties at an epitope that partially overlaps with the receptor-binding domain but is distinct from other characterised mAbs, allowing P2G3 to overcome the Omicron mutations that impair neutralisation by other anti-SARS-CoV-2 mAbs. P2G3 and P5C3 cross-neutralise each other's escape mutants so there is great potential in combining the two mAbs. P5C3 and P2G3 were licensed to Aerium Therapeutics, a biopharmaceutical company dedicated to the discovery and development of novel mAbs and antiviral treatments against SARS-CoV-2. Unfortunately, they were not taken into clinical studies. Phase 1 clinical trial conducted by Aerium showed favourable safety and PK profiles in healthy donors, but unfortunately these antibodies showed reduced potency against the XBB.1 variant and clinical development was discontinued. As the SARS-CoV-2 virus continued to evolve with greater infectivity and resistance to the humoral immune response, including all authorised therapeutic human mAbs, our groups continued to discover even more broadly active and potent patient-derived neutralizing mAbs. This work is exemplified by the P4J15 mAb, which acts as an ACE2 mimetic and prevents viral infection by binding to the Spike receptor binding domain and sharing ~93% of the buried surface area with the ACE2 contact region essential for infection of target cells. *In vitro* selection of SARS-CoV-2 mutants that escape P4J15 neutralisation showed reduced infectivity, poor ACE2 binding, and mutations that are rare in public sequence databases. Using a SARS-CoV-2 XBB.1.5 monkey challenge

model, P4J15-LS confers complete prophylactic protection with an exceptionally long *in vivo* half-life of 43 days. As such, the P4J15 mAb has potential as a broad-spectrum anti-SARS-CoV-2 drug for prophylactic protection of at-risk patient populations¹⁶.

Beyond SARS-CoV-2, the University of Utrecht CARE members focused on preparedness track mAbs for use against a future coronavirus with pandemic threat like the Porcine Delta Coronavirus (PDCoV). Four human mAbs were discovered against the viral spike protein of this emerging and zoonotic coronavirus pathogen using a humanised transgenic mouse platform. Three of these mAbs potently neutralised the authentic PDCoV viral infection in cells by blocking the virus interaction with the human APN receptor used by the virus to infect target cells. The fourth mAb, 22C10, acted through a distinct mechanism of action by binding to another spike domain and not interfering with the spike to APN receptor interaction. Several of these antibodies exhibit cross-reactivity and bind spikes from various delta coronavirus members, suggesting broader therapeutic potential for related coronaviruses¹⁷.

The development of these human mAbs is underpinned by a broad range of scientific expertise provided by the partner organisations: screening of B-cells from COVID-19 donors; identification of mAbs with the strongest affinity to viral target regions; analysis of binding properties with circulating viral variants; and assessment of virus neutralisation and cytopathic effect with assays in live virus and in a prophylactic animal challenge model of SARS-CoV-2 infection. This comprehensive approach accelerates the discovery of mAbs with broad spectrum activity, which may provide therapeutic strategies against current and future-emerging coronaviruses.

Peering into antibody-viral interactions

Access to the cutting-edge cryo-EM expertise at the University of Utrecht has been essential for CARE researchers in elucidating how antibodies bind to epitopes on SARS-CoV-2. Together with ThermoFisher and Takeda, the University developed an optimised workflow for cryo-EM coupled with state-of-the-art data collection technology that enables rapid epitope elucidation for multiple antibodies simultaneously. CARE has shown that cryo-EM can be used for high-throughput epitope mapping, with the unprecedented capability to analyse 12 antibodies in just two days¹⁸.

Developing new models to test candidate molecules

Developing *in-vivo* models for SARS-CoV-2 infection was a crucial step for CARE to allow testing of new small molecules and antibodies identified by CARE partners. The most biologically and clinically relevant animal and the most relevant/representative virus strain to mimic human disease had to be found to develop the appropriate model to assess the efficacy of candidate therapies. All of this had to be based on understanding the interactions between this new pathogen and possible host organisms.

This was breaking new ground as previously no validated models for SARS-CoV-2 infection existed. Adapting the models to new SARS-CoV-2 variants of concern throughout the project posed a further major challenge. However, the close collaboration within CARE helped to identify and characterise variants and then produce sufficiently large amounts for testing and controls. This all provides groundwork for future pandemics.

Multiple animal models were utilised: transgenic or humanised mice and Syrian golden hamsters¹⁹ for efficacy studies of our leading antiviral compounds and antibodies. Additionally, mouse-adapted SARS-CoV-2 strains were used in the mouse model^{20,21}. The non-human primate model was also established for pharmacokinetic and efficacy testing of promising candidates²². These models are very competitive in the field and proved helpful to discriminate potentially effective therapies from those unlikely to progress further. In total 10 small molecules and five antibodies were evaluated using the models in 37 experiments. The SARS-CoV-2-infected hamster challenge model demonstrated complete prophylactic protection with

P5C3¹⁴, and the non-human primate Omicron model showed complete prophylactic protection with P2G3¹⁵. Evaluating compound series at an early lead stage in these models also helped to prioritise certain compound series over others, enabling focusing of resources on those compound series with greater likelihood of success in later stage development. Data from these animal models are available through the [COVID-19 OpenData Portal from the National Center for Advancing Translational Research](#), thus serving as a resource for the global scientific community.

Deep understanding of virus-host interactions for better therapies and genetic determinants of disease

The consortium included a fully integrated system biology component, aiming to decipher coronavirus-host interactions and discover cellular pathways that are critical for virus replication, and to characterise immune response against SARS-CoV-2 and the functional implications of genetically determined disease risk and severity.

Jointly, members of the CARE consortium (Inserm and CHUV) used a systems immunology approach to identify host factors that were significantly associated with the time to illness onset, the severity of the disease and mortality of patients with COVID-19. Their findings identified CD177 as a specific marker of neutrophil activation associated with disease severity and death, which may benefit decision making in clinical practice²³. Inserm demonstrated the immunogenicity and anti-viral efficacy of a protein vaccine composed of three regions from S and one from N of SARS-CoV-2, providing a route towards a global T cell-based vaccine to counteract emerging SARS-CoV-2 variants and future SARS-like coronaviruses²⁴.

Genetic researchers at AbbVie performed ancestry-aware, trans-layer, multi-omic analyses by integrating recent COVID-19 Host Genetics Initiative genome-wide association (GWAS) data with quantitative trait loci (QTL) and GWAS endpoints that aided the identification of putative causal genes and pulmonary cells, like desmoplakin-driven IPF-shared genetic perturbations in alveolar cells²⁵.

Altogether, the systems biology team developed a comprehensive platform of complementary OMICS-based approaches such as genomics, transcriptomics, lipidomics, proteomics, metabolomics and interactomics to evaluate the physiopathology of the disease using different cell systems and for the different variants of concern, complemented by a comprehensive immunology platform and a [tool to explore COVID-19 genetic links](#). On one hand, the work gives the potential to open new avenues for antiviral therapy, on the other hand, it identified immune markers of the disease severity and progression.

Ready for clinical testing

Within CARE, a platform of five clinical centres was established, uniting the expertise of a multi-disciplinary, international team, to achieve rapid design and conduct of clinical trials. These centres are as follows:

- Goethe University Frankfurt, Germany
- Institut National de la Santé et de la Recherche Médicale, France
- Leiden University Medical Center, Netherlands
- Centre Hospitalier Universitaire Vaudois and Eurovacc Foundation, Switzerland
- Servicio Madrileño de Salud, Spain

Besides providing infrastructure for the conduct of clinical trials, this team worked to ensure quality assurance; fast track the process for submission and review of trial documents to ethics committees and of contracts to legal departments; develop patient information and ensure patient representation.

Anticipated regulatory and legal hurdles were identified and addressed by the international trial team. Certain hurdles were reduced by the new [EU Regulation 536/2014 on clinical trials in 2022](#), aiming at identical standards for conducting clinical trials throughout the European Union (EU) and [allowing](#)

[coordinated assessment of clinical trial applications between Member States](#). Nevertheless, the coordinated process under this regulation will not apply to all the steps of approval²⁶. For example, local regulations will be followed with regard to e.g., patient information leaflets and consent. Local sites may insist on using their own legal templates and acceptance of a pan-consortium site agreement template would effectively tackle a major bottleneck requiring valuable time and resources.

The service provided in this consortium allowed partners to contribute effectively and in a timely manner to the clinical trials that would potentially be conducted within CARE. The platform also aimed to offer its expertise and services to other entities that require clinical trial infrastructures with a focus on COVID-19, and to volunteers and patients with an interest in participating in clinical trials. The clinical team (through involvement in CARE's Pipeline Development Scientific Committee) were involved in the evaluation of four external antibody and four external small molecule candidates, which were assessed for trial conduct in CARE and clinical plans/protocols reviewed – unfortunately their timelines did not fit within CARE timelines for trial conduct.

Other trial options within the consortium were also considered, following discussions with both IHI and the EMA. A trial protocol was generated and set up activities are ongoing for a trial which could benefit immunocompromised patients not clearing SARS-CoV-2 (CLEAR trial).

Understanding patient preferences of COVID-19 medicines

Ensuring acceptance and clinical implementation of the small molecule and antibody compounds with their different product and treatment characteristics implies understanding of patients' views regarding these different treatments. A KU Leuven collaborated with Goethe University Frankfurt to conduct patient preference studies on COVID-19 in Belgium and Germany. This information is essential to design and select patient-relevant clinical trial endpoints as well as inform market access strategies for newly developed COVID-19 medicines.

A strong foundation enabling scientific progress

Behind the scenes, significant efforts were continuously in play to ensure the smooth running of the consortium whilst also ensuring that agreed planning, budgeting and reporting obligations were met. In addition to the more administrative aspects, the consortium also included expert support in regulatory (led by KU Leuven), ethics (led by KU Leuven), data management (led by Scifeon), communications (led by Boehringer Ingelheim and later Takeda) and legal (led by Janssen) to meet those needs as and when they arose. For the legal and ethical aspects, KU Leuven published relevant data protection issues during the COVID-19 pandemic, how ethical and legal compliance could be optimised and what the role of electronic informed consent could be.

A robust legacy for the future

One of the key lessons learned from working together in the CARE consortium was that the scientific community could organise itself quickly to respond to an urgent medical crisis. An open collaboration between pharma, biotech and academic groups (with close ties to hospitals and patients) can very effectively bring together the resources and expertise to tackle a major scientific challenge and respond quickly to the rapidly moving landscape we've faced with the SARS-CoV-2 virus.

While we have demonstrated this ability to collaborate in response to a crisis, we have additionally conducted impact analysis. The drug development activities within the CARE consortium have been represented in a system dynamics simulation model to evaluate and investigate the consortium's impact. This model enables the exploration of various scenarios regarding consortium structure and composition, offering insights and recommendations for future pandemic responses. Additionally, it captures

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