Multicentre collaboration for COVID-19 observational studies Report 4

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Study: Multicentre collaboration for COVID-19 observational studies (Report 4)

Prepared for: European Medicines Agency, Amsterdam, the Netherlands

Prepared by: E-CORE NETWORK

Report Approval and Sign-off

I confirm that I have read the contents of this report and its attachments. I approve the report in its current form.

Principal Investigator	Deborah Layton		27 September 2021
	Director of Drug Safety, EMEA Methods and Evidence Generation, IQVIA	Signature	Date
Author	Peter Egger		27 September 2021
(*if different from the Epidemiologist*)	Senior Epidemiologist EMEA Methods and Evidence Generation, IQVIA	Signature	Date
Senior QC	Hanne Ballegooijen		27 September 2021
	Senior Consultant Real World Evidence, Netherlands, IQVIA	Signature	Date

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Section 1.0 Abbreviations

Term	Definition
AC	Administrative Centre
CDM	Common Data Model
COVID-19	Coronavirus disease 2019
DA	Disease Analyser
E-CORE	Evidence for COVID-19 Observational Research Europe
EHDEN	European Health Data and Evidence Network
EMA	European Medicine Agency
HM	Hospital de Madrid
IMRD	IQVIA Medical Research Data
IPCI	Integrated Primary Care Information
LPD	Longitudinal Patient Database
OHDSI	Observational Health Data Science and Informatics
OMOP	Observational Medical Outcomes Partnership
SAB	Scientific Advisory Board
SAP	Statistical Analysis Plan
SCC	Study Coordinating Centre
SIDIAP	Information System for Research in Primary Care

Section 2.0 Executive summary

This report first provides a brief summary of the E-CORE network set-up including the proof of concept study to pilot the network as described in Report 2 using data sources described in Report 1 and secondly outlines the evaluation of the efficiency of the network collaboration. The evaluation emphasises key learnings and insights based on the experiences of the current project and focuses on recommendations for the future of the network including future projects. The evaluation report is structured into five areas: network infrastructure; enrolling new data partners; the proof of concept study; the role of the EMA; sustainability of the network.

The four key components of the network infrastructure, Administrative Centre (AC), Study Coordinating Centre (SCC), Scientific Advisory Board (SAB) and Data Partners have proved to be a sufficient and appropriate organisational set up for the successful operation of the network collaboration. The intent is for the SCC to be chosen on a study-by-study basis while the other three member teams are permanent. Close interactions between the AC (which is the general secretariat for communication, data sources onboarding and tracking studies) and SCC (which leads study execution including project management) are important for an efficient execution of a research project, as is an SCC that has extensive experience in conducting network studies in the OMOP environment. The SAB has an important role to play, both in the overall governance of the network as well as in providing scientific advice as needed for individual research studies.

All data partners were newly enrolled into the network for the purpose of the proof of concept study. Ideally, data partners are enrolled in the network up-front and with a master agreement, to speed up and ease the process of data sources inclusion for a particular research study. Participation in other networks, such as EHDEN, greatly facilitates enrolment in E-CORE. Data partners' familiarity with OMOP and conducting network studies is important and training and support needs to be provided by the SCC and SAB if necessary.

The proof of concept study, as detailed in the study protocol (http://www.encepp.eu/encepp/viewResource.htm?id=41699), served as a pilot project to test the E-CORE network capabilities. The scientific aim was to evaluate the pattern of COVID-19 treatment and adverse medical events in diagnosed COVID-19 patients from across Europe and beyond. A total of ten primary care and hospital care data sources from seven European countries and the US were included in the study. To date, the project has been considered a success, thus far addressing the framework objectives (which were establishing a library of cohorts of COVID-19 patients, developing a collaborative framework across the data network and conducting a proof of concept study to test the network capabilities). A number of critical success factors of the proof of concept study were identified: clear study objectives with agreed upon standardised output that makes full use of the OHDSI tools; use of the OMOP cohort diagnostics tool to ensure comparable study cohorts across the data sources; detailed data requirements at study inception to ensure most appropriate data sources inclusion from the outset; keep updates of the analyses to a minimum; dedicated epidemiologic and clinical expertise at the local level to help the local implementation of the data query and interpretation of the results; regular meetings between the SCC and data partners on work progress and to solve common problems.

The project highlighted several key aspects regarding E-CORE sustainability. A clear value proposition for data partners to join the E-CORE network is crucial. A web-based searchable catalogue listing the network data sources including key meta data help promote the network as well as initial study feasibility assessments. Extensive use of the OMOP tools for data query and analysis provides the required scalability of research work in the network. The network is to be funded through project fees and other grants. The EMA has the potential to be a significant ambassador for the network and while the EMA cannot mandate use of the network for COVID-19 studies, project endorsement by the EMA helps local acceptance and study approvals.

Section 3.0 Background

The project E-CORE was set up to monitor the efficacy and safety of COVID-19 treatments when used in day-to-day clinical practice. This was to be achieved through a multinational research network that utilises existing healthcare data from a variety of healthcare institutions in the primary care setting and hospital setting throughout Europe and US. The project started in 2020 with the establishment of the network including its membership and governance framework. Reports 1 and 2 describe the included data sources and the network set-up including governance respectively. A proof of concept study was then set up to pilot the use of the network by addressing the following research topics (as detailed in the study protocol - http://www.encepp.eu/encepp/viewResource.htm?id=41699): describe utilization of systemic glucocorticoids for treatment of COVID-19 in hospitalized and ambulatory settings within 90 days following COVID-19 diagnosis; describe the patient population; assess adverse events of interest, mortality and other disease outcomes. Following completion of the study it was important to conduct an evaluation of the network set-up and its research collaboration to provide recommendations for future research studies on COVID-19 within E-CORE.

Section 4.0 Aim and objectives

Report No.4 comprises the evaluation of the efficiency of the E-CORE collaboration between the SAB, scientific experts and data partners that provide data sources enabling COVID-19 research for pharmaco-epidemiological studies. This includes the assessment of the mechanisms by which a new data partner can enter the network and how a study is set-up and can be run using the network.

The specific objectives of this report are to evaluate:

- the structure and governance of the network including enrolment of new data partners (Sections 7.1 and 7.2)
- the process of conducting a study in the E-CORE network (Section 7.3)
- the sustainability of the network (Sections 7.4 and 7.5)

based on the experiences and learnings from the proof of concept study.

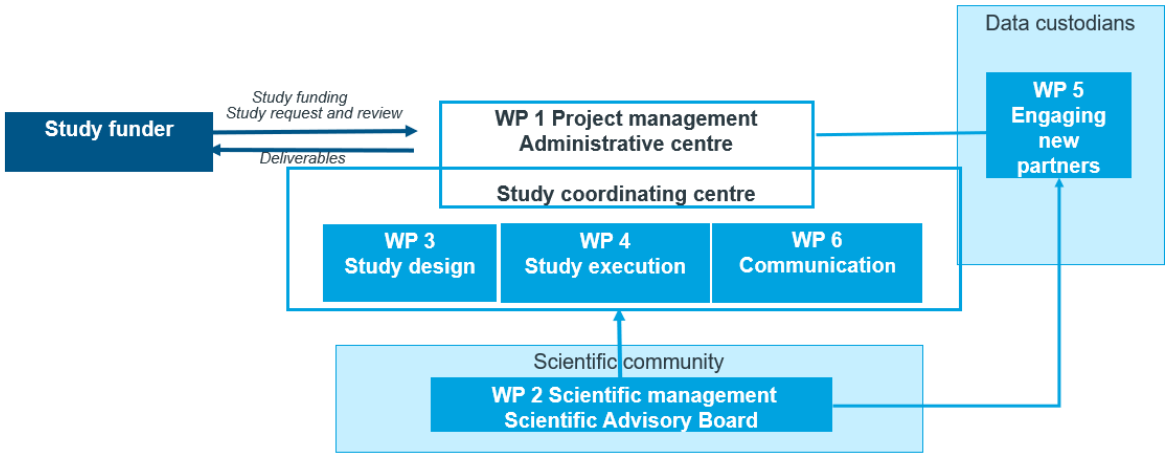
Section 5.0 E-CORE set-up

This section contains a summary of E-CORE as described in Report 2. and provides the background for the evaluation of the efficiency of the network collaboration.

5.1 Structure and governance of the network

E-CORE is a collaboration between multiple institutions. Figure 1 describes the key components of the network and its governance model and provides an overview of the collaborating stakeholders and their relationships within the network.

Figure 1. Governance model for the E-CORE network



Administrative Centre (AC)

The Administrative Centre resides at IQVIA and has the following responsibilities:

- provide the general secretariat for internal and external communications
- support outreach to additional data sources and onboard new data partners in the network
- triage incoming study requests and track study requests and study execution.

Study Coordinating Centre (SCC)

The SCC will be assigned on a rotating basis for each study and provides the study lead responsible for:

- study project management including study contracts
- study execution.

Network partners volunteer to be an SCC for a specific study, to be decided by the SAB by consensus.

Data Partners

Main responsibilities are to:

- ensure data quality and database mapped in CDM
- serve as study investigator: provide expertise on their data, execute feasibility queries, provide input in the study design, obtain local governance and ethics approval, execute the study analysis and support results dissemination.

Scientific Advisory Board (SAB)

The SAB is formed by scientific subject matter experts including data partners, with the following responsibilities:

Decision making on

- acceptance of a study and nomination of the SCC
- addition of SAB members
- addition of data partners.

Advice and coordination on

- study design, execution and dissemination of results, when required
- communications and further development of capacity and methods in general.

5.2 Enrolling new partners in the E-CORE Network

Any data source that is mapped to the OMOP CDM can participate in E-CORE. The two extensive networks OHDSI and EHDEN provide a large pool of data source candidates comprising both primary and secondary data from Europe. A detailed list of inclusion criteria is included in Report 2. A key criterion for inclusion in E-CORE is the presence of a sufficient number of COVID-19 patients in either in-patient or ambulatory settings as well as essential variables needed to conduct COVID-19 related research (e.g., COVID-19 disease history, disease presentation, laboratory test of COVID-19, and treatment of COVID-19 including medicines and oxygen therapy).

5.3 Data ownership and access, privacy and security

E-CORE operates in a federated (distributed) access model. Data partners remain in full control of their institutional data, both raw and in the OMOP CDM. To generate the results, each data partner executes a R package against their database. Only aggregated statistics will be shared via a secured repository. All study documentation including aggregated results will be archived on a specific and secured drive centrally at the SCC and retained for a period of five years in accordance with Good Pharmacoepidemiology Practice (GPP) guidelines. Protection of patient privacy and general data security regulations is the responsibility of the data partners. E-CORE obligates each data partner to abide by the local and EU-wide data privacy rules and regulations. In general, only the required personnel have access to the data or study documents, which are to be stored in a secure environment. Aggregated results are transferred to the SCC using appropriate encryption. The protocol and study results will be made public by the SCC and stored in the EUPAS register.

5.4 The process of conducting a study in E-CORE

Study initiation to completion involves the following steps:

- Contacting the E-CORE network with a research question for a study proposal
- Finalising the full research project and contracting
- Setting up the study team and identifying available data sources
- Generating the study protocol and the statistical analysis plan
- Ensuring ethics compliance and data protection
- Executing the study
- Reporting of study results and publication.

5.5 Sustainability of the Network

The E-CORE network is a publicly/private funded project that was started and initially funded by EMA. The aim is to have a medium to long term sustainability of approximately 3 to 5 years by inviting new Study Funders from both the public as well as the private sector to use the network for COVID-19-related research.

Overview of participating data partners whose study results were included in the project.

Database	Managing Organisation	Country	Covered Patient Lives (million)	Data available from
LPD France	IQVIA	France	7.8	1994
DA Germany	IQVIA	Germany	34	1992
University Hospital Germany	University of Dresden	Germany	0.5	2012
LPD Italy	IQVIA	Italy	2	2004
IPCI	Erasmus MC	Netherlands	2.6	1996
Clinical Center Serbia	Clinerion	Serbia	0.4	2004
SIDIAP	IDIAP Jordi Gol	Spain (Catalonia)	7.8	2006
Parc Salut Mar Barcelona (IMASIS)	Parc Salut Mar Barcelona	Spain	1.5	1990
UK IMRD	IQVIA	UK	15	1996
Hospital Charge Data Master	IQVIA	US	86	2007

Section 6.0 The proof of concept study

This section summarises the proof of concept study, as described in the study protocol (http://www.encepp.eu/encepp/viewResource.htm?id=41699).

Title:

Systemic glucocorticoids in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients, within primary and secondary care settings

The aim of this study was to describe patterns of systemic glucocorticoid use, as well as the risks of adverse events associated with these medications, in patients with either a first confirmed diagnosis for COVID-19 or a first positive PCR test for SARS-CoV-2 using healthcare databases from seven European countries.

Primary Objective:

Utilization of systemic glucocorticoids (e.g., dexamethasone, prednisolone, methylprednisolone or hydrocortisone) for treatment of COVID-19 in hospitalized and ambulatory settings within 90 days following COVID-19 diagnosis:

- prevalent or incident use at diagnosis
- co-prescribing and other respiratory support
- type of medication
- time to initiation
- route of administration
- daily dose at initiation and cumulative dose
- previous glucocorticoid use: current (≤15 days), recent (15-30 days), remote (>30 days prior).

Secondary Objectives:

1. Describe the patient population: demographics; comorbidities; symptoms preceding and/or on the date of diagnosis; time from onset of symptoms to diagnosis.
2. Quantify the incidence rates and time to onset of adverse events of interest (eg. infections, hyperglycaemia, GI bleeding, composite of cardiovascular disease events) within 30 and 90 days post treatment start.
3. Quantify the incidence rates of mortality and other disease outcomes within 30 and 90 days post treatment start.
4. Explore the performance of different coding definitions for COVID-19 and how they influence the size of the cohort.

Study design:

A descriptive cohort study design using secondary data healthcare records.

Setting and data sources:

COVID-19 diagnosed patients across primary and secondary care settings in the following European Countries were considered: France, Germany, Italy, Netherlands, Serbia, Spain and the United Kingdom. A hospital data source from the US was also included. The study time period included 1st January 2020 to 1st January 2021, with cut-off dates for data inclusion varying by database. Four different cohorts based on healthcare setting (ambulatory or hospital setting)

and systemic glucocorticoid user type (naïve or prevalent) were created. The data sources are listed below:

Primary/Ambulatory care:

- France, Italy – IQVIA LPD
- Germany – IQVIA DA
- The Netherlands – IPCI
- Spain – SIDIAP
- United Kingdom – IMRD

Hospital care:

- Germany – University Hospital
- Serbia – Clinical Center Serbia
- Spain - Parc Salut Mar Barcelona (IMASIS)
- US – Hospital Charge Data Master.

Variables:

Demographic and clinical

- age, sex, month of diagnosis, comorbidities

Disease severity

- Ambulatory: Hospital admission, venous thromboembolism or pulmonary embolism, disseminated intravascular coagulation, death of any cause
- Hospital: Intensive services as an outcome in inpatient cohorts (including mechanical ventilation and Extracorporeal membrane oxygenation (ECMO)), venous thromboembolism or pulmonary embolism, disseminated intravascular coagulation, discharge from hospital, death of any cause

Treatment

- Glucocorticoids used in COVID-19: dexamethasone, prednisolone, prednisone, methylprednisolone or hydrocortisone
- Glucocorticoid for pre-existing conditions
- Other COVID-19 treatments (e.g., antiviral, antibiotic, statin therapy)
- Respiratory support

Adverse Events

- Composite cardiovascular events, hypertension, arrhythmia, gastritis, gastric ulcer, GI bleed, psychosis, myopathy, hyperglycaemia and any bacterial viral, fungal and parasitic infection.

Data analysis:

Continuous and categorical variables were described using the appropriate statistical measures. Time to event analysis comprised incidence rate estimates including 95% CIs, Kaplan-Meier graphs as well as Cox regression models that included adjustments for potential confounders. The results for each country and setting were presented separately.

Study Coordinating Centre for the project:

The Study Coordinating Centre activities were executed by IQVIA and as such is responsible for the proof of concept study as a whole.

Section 7.0 Evaluation of the Collaboration

The Evaluation of the Efficiency of the Collaboration focusses on key learnings and insights based on the experiences of the current proof of concept study. This evaluation report has a focus on the future by providing key recommendations for the network including future projects. For this report several stakeholder interviews were conducted. This included the SAB, data partners, EMA and AC and SCC members. These interviews together form the basis of this report. The evaluation focusses on five domains

1. Network infrastructure
2. Enrolling new data partners
3. Execution of the proof of concept study
4. The role of the EMA
5. Sustainability of the network

7.1 Network infrastructure

The four key components of the network; AC, SCC, SAB together with the data partners proved to be a sufficient and appropriate organisational set up for the successful operation of the network collaboration. The set-up is simple, with the four pillars being able to cover all essential aspects of the operation. Specific observations and recommendations are:

- The AC is there to support the SCC. Close collaborations and seamless interactions between the AC and SCC are essential for the smooth running of a research project. Weekly project update meetings where work progress is tracked, and any issues identified and addressed were important to keep the project on track.
- It is crucial for the SCC to have in-depth experience in conducting multi-database network studies within the OMOP environment. This includes expertise in using the OMOP CDM as well as utilising the OHDSI tools for data analysis.
- Scientific oversight and support by the SAB including assistance in any OMOP/OHDSI-related questions is invaluable and essential for the smooth running of the project. To this end, the bi-monthly meetings that took place between the SAB and SCC were important to track study progress.
- The SAB role in evaluating the scientific merit and suitability of a requested research project for E-CORE in consultation with data partners and confirming an appropriate SCC has yet to be tested as the current proof of concept study was part of setting up the network.
- A clear definition of roles, tasks and responsibilities between the different members of the network is vital.

7.2 Enrolling new data partners

All data partners were newly enrolled into the network for the purpose of the proof of concept study. Hence, for each data partner the enrolment process started from the very beginning and the project timelines had to take that into account. For data partners with experience in network studies and OMOP, enrolment in E-CORE was more straight-forward than for data partners who were new to a network study and specifically not transformed in OMOP. Some data partners participated in the proof of concept study without funding as they were enrolled later in the proof of concept study and there was no budget. Voluntary participation is not a suitable framework to ensure sustainability. Also, ideally, data partners are enrolled in the network up-front and with a master agreement, to speed up and ease the process of data sources inclusion for a particular research study. The Sustainability section below will further discuss up-front enrolment of data partners. Specific observations of the enrolment process are listed below:

- Participation in other networks, such as EHDEN, greatly facilitates enrolment in E-CORE, as the data are likely to be available in a CDM and have undergone data quality evaluations, local study approval is also likely to be easier and network contacts already exist.
- In addition to having the database mapped to the OMOP CDM, it is important for data partners to have experience in conducting studies within the OMOP environment (e.g. running R-packages, QC of results, being aware of the ethical submission requirements). Where necessary, the SCC needs to provide training to data partners to rapidly gain this expertise as well as respond to any queries.
- Setting up the study contract with data partners can be a lengthy process. Enrolment of new data partners should include a Master Agreement that takes into account local requirements, to facilitate and simplify the process of setting up subsequent study-specific contracts.

7.3 The proof of concept study

The research project serves as a proof of concept project of the E-CORE network collaboration. The scientific aim of the study including objectives and the study design were summarised in Section 6 above. The IQVIA team provided the SCC responsibilities, which included leading protocol and SAP development and project management. The study protocol was reviewed and endorsed by the SAB and the study funder EMA. Study execution included newly recruiting multiple data partners into the network, with the majority recruited at study start and some after study start in response to the EMA request for more hospital data sources and for non-EU data sources. One data partner withdrew from the study early on due to lack of resources (SNDS Lyon France). Some of the data partners participated in a network study within the OMOP environment for the first time and therefore needed more time than others to be ready to run the study.

The following data sources contributed with results in the study:

Primary/Ambulatory care:

- France, Italy – IQVIA LPD
- Germany – IQVIA DA
- The Netherlands – IPCI
- Spain – SIDIAP
- United Kingdom – IMRD

Hospital care:

- Germany – University Hospital
- Serbia – Clinical Center Serbia
- Spain - Parc Salut Mar Barcelona (IMASIS)
- US – Hospital Charge Data Master

To date, the project has been considered a success, thus far addressing the framework objectives (which were establishing a library of cohorts of COVID-19 patients, developing a collaborative framework across the data network and conducting a proof of concept study to test the network capabilities). The proof of concept study results will be included in the Final Study Report in Report 3 and it is the intention to present them in scientific conferences and publish them in multiple scientific papers.

Below are specific observations and recommendations based on experiences of the research study:

- Clear and precise study objectives and a detailed study design, as outlined in the current study protocol, greatly helps achieve the same understanding of the study and avoids different interpretations by different project partners.
- Standardise study queries and the analysis steps as much as possible to maximise the utility of the OHDSI tools and reduce bespoke work. The result is a shorter project duration and the same approach across all data sources and fewer potential errors. This is an important factor in making the E-CORE network scalable.
- Specify the data requirements as detailed as possible at the beginning, including the required granularity of specific data items, so that data source suitability and any potential shortcomings can be established at the very beginning, saving valuable project time and resources.
- A project kick-off meeting with all project members is important, to establish contacts and explain the overall scope and scale of the project. Not all project members were able to attend the kick-off meeting of the current project and an option could have been to hold a follow-up meeting for this purpose. Also, the opportunity for study participants (and, in particular data partners) to consult members of the SAB in addition to the SCC on project queries when necessary, greatly enhances project execution.
- It is important to have regular meetings between the SCC and all participating data partners throughout the project duration to provide updates on study progress and discuss any issues on the local implementation of the data queries.
- Data partners should also endeavour to meet amongst themselves, facilitated by the SCC, to share best practice and discuss potential problems. This will help especially those data partners with less experience in conducting network studies within the OMOP environment.
- Data query and analysis:
    - Extensive use of the cohort diagnostics package at the beginning helps confirm the most appropriate case definition and establish the most comparable study cohorts across the different data sources.
    - Data analysis may evolve during the project duration. It is important to keep the updates of the data analyses to a minimum as each update requires a rerunning of the analyses by each data partner. After an initial test run, there should be one final version of the

analysis package (the R-Package), that needs to be run only once at the local data source level.

    - QC of the results by the partners is burdensome especially for large studies and can benefit from a web application to facilitate the review.

- It is important to have dedicated epidemiologic and clinical expertise available at the data partners to provide an expert local perspective on medical definitions and data queries, help interpret the study results and propose study improvements.
- It is imperative to establish a publication strategy at the outset to which all the parties (including EMA) sign up. In the first instance the SCC could present a proposed strategy at the kick-off meeting for discussion and approval.

7.4 The role of the EMA

It is important that the role of the EMA in E-CORE is clarified, both for the network overall including infrastructure and governance and for the individual projects. The list below includes some observations:

- The EMA has the potential to have a significant impact as an ambassador for the E-CORE network collaboration.
- The individual E-CORE projects greatly benefit from EMA involvement and visibility: EMA project endorsement helps getting the projects accepted by authorities at the local level.

7.5 Sustainability of E-CORE

This section discusses E-CORE team members' perspectives on the sustainability of the network for future COVID-19 studies, based on the experiences from the current project.

- The success of the network depends on the availability of a wide range of data sources from across Europe and beyond and the data partners' willingness to participate in the network studies. To achieve this, a clear value proposition for data partners to join the network is important.
- Network sustainability also depends in part on the effective use of the OMOP CDM and OMOP tools for data query and analysis. The OMOP environment and tools facilitate scalability of the collaboration and enable the conduct of multiple research projects simultaneously. This includes extensive standardisation of the different project steps from project initiation to the final study report.
- A network data catalogue containing key meta data for all included data sources could be an effective way to further promote the network in the scientific community. Also, it would provide an important and low-resource starting point in the selection of suitable data sources for a new study within the network.
- The network needs to be funded through project fees including research and other grants. A subscription model can also be considered as part of the finance model.

- The EMA agree to be part of the network, provide input in its' governance and be a general ambassador of E-CORE. Also, it will provide project endorsement, which can be used to help local project approvals.
- The EMA cannot allocate studies to E-CORE or mandate projects to use the network. Furthermore, the EMA cannot be involved in the study execution, including interpreting the study outcomes and disseminating the results. However, The EMA could endorse the E-CORE as a Network of Excellence.
- High-quality scientific research is an effective way of promoting the use of E-CORE.
- It is important to collaborate with other networks and make use of their capabilities if possible. In particular, the EHDEN project should provide a main source for recruiting new data partners. Also, possibilities for a link-up and a potential integration in other, wider-ranging networks such as the upcoming DARWIN project should be explored in the future.