Multicentre collaboration for COVID-19 observational studies Report 2

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Study: Multicentre collaboration for COVID-19 observational studies (Report 2)

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Section 1.0 Abbreviations

Term	Definition
CDM	Common Data Model
COVID-19	Coronavirus disease 2019
DQD	Data Quality Dashboard
E-CORE	Evidence for COVID-19 Observational Research Europe
EHDEN	European Health Data and Evidence Network
EMA	European Medicine Agency
HM	Hospital de Madrid
IMI	Innovative Medicines Initiative
IMRD	IQVIA Medical Research Data
IPCI	Integrated Primary Care Information
LPD	Longitudinal Patient Database
TNF	Tumour Necrosis Factor
OHDSI	Observational Health Data Science and Informatics
OMOP	Observational Medical Outcomes Partnership
QC	Quality Control
RCT	Randomised Clinical Trial
SAB	Scientific Advisory Board
SIDIAP	Information System for Research in Primary Care

Section 2.0 Executive summary

Coronavirus disease 2019 (COVID-19) is an emerging and rapidly evolving infectious disease that has reached pandemic status. It also poses a major global challenge to health-care systems, which have either been partially or completely disrupted in many countries due to overwhelming demand.

In June 2020, EMA contracted IQVIA with a project to build a framework for the conduct of multicentre cohort studies on the use of medicines in COVID-19 patients. This project is based on the resources from the OHDSI and EHDEN networks, forming the E-CORE network, by using databases harmonised to the OMOP CDM and existing analytical tools and processes to accelerate the generation of robust real-world evidence about the utilisation, effectiveness, and safety of medicines for the treatment of COVID-19.

We had previously developed Report No.1 which describes the landscape for assessing electronic medical databases from at least seven European countries, the quality checks applied to the enrolled databases and the feasibility of conducting future observational COVID-19 studies in this network.

This Report No.2 provides a high-level understanding of the E-CORE network and guidance on how to conduct a network study in this framework. We describe the structure of the project including seven work packages, governance, how to enrol new data partners and the process of running studies in six steps within E-CORE. All databases have been mapped to the OMOP common data model (CDM) to enable common federated analytics.

This network aims to have medium to long term sustainability and should enable accelerated generation of evidence about the utilisation, effectiveness, and safety of medicines for COVID-19 patients. This will help to improve the understanding of the treatment and care for these patients.

Section 3.0 Background

COVID-19 is an emerging and rapidly evolving infectious disease that has reached a pandemic status. As of 4th December 2020, more than 65 million people worldwide (~18 million people in Europe) were diagnosed with COVID-19 (ECDC 2020), whilst the number of deaths has reached over 1,507,000 worldwide and 431,000 in Europe (ECDC 2020). COVID-19 poses a major global challenge to health-care systems, which have either been partially or completely disrupted in many countries due to overwhelming demand, healthcare workers getting sick and resource diversion (WHO, 2020).

As part of the search for a cure for COVID-19, existing drugs were repurposed with various results. For example, two antimalarial drugs (chloroquine and hydroxychloroquine) showed initial promise but failed to show efficacy in further studies (Torjesen, 2020). Reports on angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-II receptor blockers were initially inconsistent, (Meng et al., 2020; Zhang et al., 2020), whereas lately a lack of effectiveness was shown (Li, Wang, Chen, Zhang, & Deng, 2020; (Morales et al. 2020). Other classes of drugs that show potential include interleukin-6 receptor (IL-6R) antagonists, interleukin (IL)-1 antagonists, tumour necrosis factor (TNF)-alpha inhibitors, and Janus kinase inhibitors (Sarzi-Puttini et al., 2020).

Besides efficacy, drug safety is another major aspect of medical therapy that drives medical decision making. This is especially true when the benefit-risk balance is uncertain and in vulnerable patients. Although RCTs are routinely used to investigate efficacy and safety, the long-term safety outcomes and adverse drug reactions with a low incidence are usually not captured and certain at-risk categories of patients are often excluded. Moreover, although the speed of running an RCT has increased significantly in the context of the pandemic, they are still challenging to conduct as healthcare institutions tend to either be overwhelmed in areas of surge or lack patients where lockdown measures have managed to control the virus. Therefore, RCTs need to be rapidly complemented by observational database studies, especially in the area of safety and for populations excluded from clinical trials, such as patients seen in primary care. Indeed, the majority of COVID-19 patients are treated in the primary care setting.

In this environment, multinational research networks dedicated to observational studies are essential. They can provide valuable insight through comparison between different institutions from different countries, and therefore validate true clinical findings from artefacts due to different healthcare settings and data capture modalities. For example, the International Coalition of Medicines Regulatory Authorities (ICMRA), of which EMA is a member, acts as a forum to support the coordination and cooperation among global medicine regulatory authorities to expedite the development, authorisation and availability of COVID-19 vaccines and treatments.

During 2020, EMA raised several tenders to support the monitoring of the efficacy and safety of COVID-19 treatments and vaccines when used in day-to-day clinical practice.

As part of this initiative, E-CORE (**E**vidence for **C**OVID-19 **O**bservational **R**esearch **E**urope), was designed as a network for the conduct of multicentre cohort studies on the use of medicines in COVID-19 patients. The E-CORE network aims to establish a sustainable framework to support the rapid provision of real-world evidence on the utilisation, effectiveness and safety of therapies for COVID-19 patients within Europe.

Section 4.0 Aim and objectives

Report No.2 describes the **E-CORE** network, which is a collaboration between data partners and scientific experts that provide data sources enabling COVID-19 research for pharmaco-epidemiological studies. This report acts as a high-level guidance document for the E-CORE network and describes the mechanisms by which a new data partner can enter the network and how a study is set-up and run within the network.

The specific objectives of this report are to describe:

- The structure and governance of the network (Section 5.0)
- The process of conducting a study in the E-CORE network (Section 6.0)
- The plans for sustainability of the network (Section 7.0)

Section 5.0 E-CORE Network Structure and Governance

5.1 Structure and governance of the network

E-CORE is collaboration between multiple institutions: academics, CROs and data partners with expertise in conducting pharmacoepidemiological studies, data access and conduct of multinational studies.

As all studies run in a network require participation and input from several stakeholders, a governance structure has to be developed. Figure 1 describes the governance model for E-CORE and provides an overview of the collaborating stakeholders, their relationships and work packages (WPs) within the network.

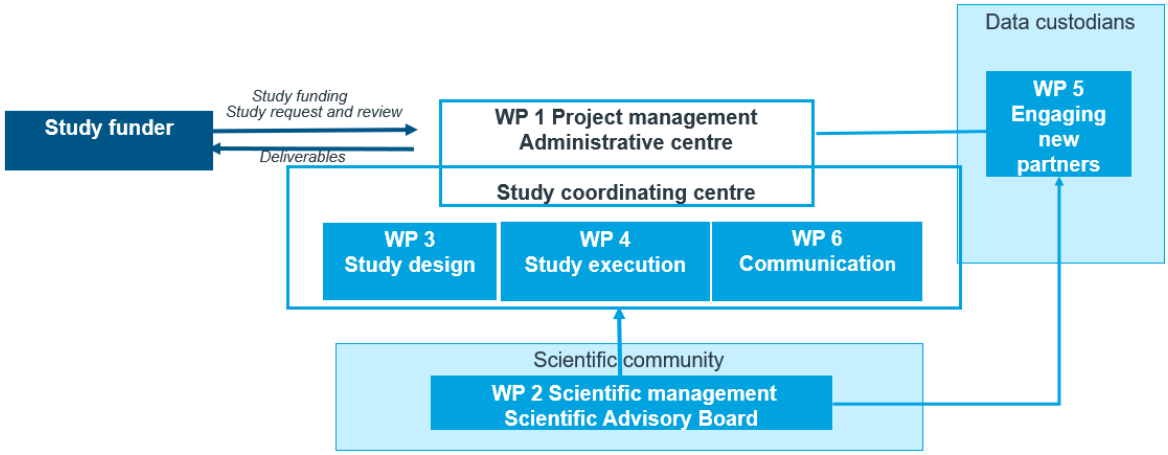

Figure 1. A generic governance model for the E-CORE network

Governance Model

The governance model describes the structure for running the E-CORE network and has the following characteristics:

- It includes an Administrative Centre and a distributed network of stakeholders/researchers with access to databases which are called ‘data partners’
- It includes a Scientific Advisory Board (SAB) in charge of providing scientific advice
- Most of the roles are not fixed between projects and the partners can take multiple and different roles during a specific study conduct
- Multiple studies can be run in parallel

Administrative Centre

The Administrative Centre will be set up at IQVIA and will be the main contact point for the Study Funders, potential external partners or media queries.

Responsibilities:

- Triage incoming study requests and is the initial point of contact for funders or media queries

- Coordinate SAB meetings and data partner meetings, independent of a specific study (e.g., study triage meeting, method development meetings)
- Onboards new partners in the network (e.g., offers trainings and support with running R packages or completing documentation) and collaborates with WP5 to engage new partners
- Maintain a centralised tracker of study requests, progress and deliverables submission, including the compliance of each study with the minimum criteria for acceptability in the network (see Appendix 1)
- Develops the communication plan and is in charge of any queries related to the network or studies (in collaboration with the Study Coordinating Centre and Study Funder)

Study Coordinating Centre

The Study Coordinating Centre will be assigned for each study and its main role is to ensure the completion of the study in time and with quality. It will be assigned on a rotating basis for each study, any partner can volunteer to become the Study Coordinating Centre for a specific study (see below). This would maximally leverage domain expertise and resources and result in better scalability.

As a minimum, the Study Coordinating Centre will have the following responsibilities:

- Drafting of contracts (see Contracting) and responsible for the execution and delivery (see Section 6)
- Study project management: in charge of resource allocation among partners, delivery coordination and financial management of the project

Optional

- Study conduct - The Study Coordinating Centre's involvement in the study can vary from administrative and technical involvement in running the study to coordinating function only. This can differ between studies and will be decided upfront before starting a new project. The degree of involvement in running the study in collaboration with other partners has to be agreed upfront. A pre-agreed share of the funding will be allocated to the Study Coordinating Centre.

How the Study Coordinating Centre is assigned

After a study is triaged by the Administrative Centre, an initial meeting with SAB members and active data partners takes place (study triage meeting). The final go/no go decision whether to run a study will be taken during this meeting, considering if the network has adequate data and resources to run the study, if timelines can be met and if the budget is enough for the study. Any partner can volunteer to become the Study Coordinating Centre for a specific study if they have at least one year in the network and have the experience and resources to do so. They will submit their intent by email to the SAB before the meeting. The decision to assign the study coordinating role will be taken by consensus from the SAB during the study triage meeting.

If only one partner volunteers, it will be assigned the study coordinating role providing it can show capacity and expertise.

NB: The core partners of E-CORE, University of Oxford, Erasmus University Medical Centre, IQVIA and SIDIAP are already each considered to fulfil the criteria for being a Study Coordinating Centre.

Data partners

Data partners are E-CORE partners that contribute with data to the network. The main responsibilities of the data partners network are:

- Responsible for the data quality and updating of their database mapped in CDM
- Provide expertise on their data
- Execute feasibility queries to decide on participation in a specific study
- Provide input to protocol, cohort definitions, report and other study deliverables if required to do so
- Obtaining local governance and ethics approval
- Serve as investigator and execute common analytics on the data, approve the aggregated results, and return those to the study coordinator
- Provide input in the process of dissemination of results

Scientific Advisory Board (SAB)

The scientific advisory board is formed by internal and external scientific subject matter experts in pharmacoepidemiology, clinical research, regulatory science and statistics. Some of the SAB members are also data partners. Currently SAB is composed by six founding members and can incorporate future partners (if needed).

Founding SAB members are:

- Sam Salek, Prof. Pharmacoepidemiology, University of Hertfordshire, UK
- Daniel Prieto Alhambra*, Prof. of Pharmaco- and device epidemiology, University of Oxford
- Peter Rijnbeek*, Associate Prof. Health Data Science, Erasmus University Medical Center
- Deborah Layton, Prof. at University of Keele and Drug Safety Director at IQVIA
- Christian Reich* - VP Technology Consulting at IQVIA
- Talita Duarte Salles*, Epidemiologist at IDIAPJordiGol

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* also data partners

If a network member wants to join the SAB, it needs to have been in the network for at least one year as a precondition and submit a letter of intent which shows capability and commitment and a resume of the main scientific point of contact to the core SAB. The core SAB will make the decision whether to admit a new member or not as part of SAB. The membership will be renewed every year, with a similar process.

If one of the core members resigns or leaves the network, he/she can recommend a replacement from the same institution (if the institution stays in the network) or another non-core member from the existing ones will be sought to replace him her.

SAB is having both a decision-making role and an advisory role as detailed below:

Decision making

- During the study triage meeting, whether a study will be performed by the network or not.
- Who will be the Study Coordinating Centre for a specific study after examination of all proposals - for the decision of the Study Coordinating Centre, only one representative from the same organisation can vote.
- Addition of SAB members.
- Addition of data partners.

Advise and coordination

- Ongoing throughout the entire project, when required.
- Publication strategy and communications in conjunction with WP6.
- Further development of capacity and methods independent of any study.

Note the final decision on study design, running the analysis, code lists and publication stays with the Study Coordinating Centre, while the SAB only has an advisory role.

The SAB takes decision by consensus and each meeting should have at least 50% of its members present.

Study Funder

The Study Funder will be required to sign the contract, provide study funding, review and accept the study deliverables, and provide input on the communication plan.

The contractual arrangement between the Study Coordinating Centre and the Study Funder should be signed prior to the first step in the research process. More details in Section 6.3 Contracting.

The content of the research project and the potential contribution to the study design and protocol, including the analysis plan, shall be established by agreement between the Study Funder and the Study Coordinating Centre. However, the Lead Investigator (see below) is ultimately responsible for the design of the protocol, the conduct of the study, the analysis and interpretation of the study results and the preparation and publication of the study outcome.

If the funder requests a new analysis during the protocol writing stage, which was not defined in the proposal, this will require a change order.

The Study Funder shall be entitled to view the final results and interpretations thereof prior to submission for publication and to comment in advance of submission within a reasonable time limit, as agreed in the research contract and without unjustifiably delaying the publication.

Lead Investigator

This is an individual assigned by the Study Coordinating Centre. He or she should be a person without financial, commercial or institutional interests in any particular outcome of the study (EMA 2018), having the following responsibilities:

- To sign the contract with the Study Funder.
- To sign all the study deliverables and assume the final responsibility for their content.
- To be responsible for the design of the protocol, the conduct of the study, the analysis and interpretation of the study results and reporting.
- To ensure that the study meets regulatory requirements and that the final protocol, including protocol modifications, is agreed between the Lead Investigator, the Study Funder, and the funder.
- To keep the funder informed about the study progress.
- To not communicate results, other than final or scheduled interim results.

Work packages (WPs)

The E-CORE network is divided into six WPs, each addressing different aspects of the collaborative framework. Partners will take part on different WPs as appropriate.

These WPs entail the following:

- WP 1 Project Management

This WP includes both the Study Coordinating Centre and the Administrative Centre, responsible for project and network management respectively whose roles are described in section 5.0. They are included in the same WPs due to the close collaboration required between those.

- WP 2 Scientific Management

WP 2 involves the SAB and among other tasks, decides together with the data partners, whether the E-CORE network can adequately answer the question(s). More details on the roles and responsibilities in section 5.0 under SAB.

- WP 3 Study Design

WP 3 is formed by one or more partners who are contracted for the study design. WP 3 includes translating the study question into research objectives and writing the study protocol and analysis plan.

- WP 4 Study Execution

WP4 is formed by one or more partners who are contracted for the study execution. WP3 and 4 are collaborating closely in translating the analysis plan into the programming code. Creation of cohort definition and diagnostics necessary for the database interrogation are part of WP 4 and well as the development of programming code, distributing the code to the data partners and together with the Administrative Centre, supporting data partners with running the code.

- WP 5 Enrolling new partners

This WP engages new partners in the network as the network evolves. This includes the quality check of data partners, as described in Report 1. It is highly desirable to engage data partners that have their data mapped to OMOP CDM and enrolled into an E-CORE study before, particularly due to the urgency of this research given the COVID-19 pandemic. New data partners which want to join and convert their data might be referred to the EHDEN open calls for financial support and the engagement of certified

specialty Small and Medium-sized enterprises. Data partners can only join E-CORE after mapping their full database to the OMOP CDM.

The decision to engage a new partner must be taken by the SAB. Administrative support for enrolling new partners comes from the Administrative Centre. More details in section 5.2

- WP 6 Communication

WP 6 is responsible for compiling the research results into one final report and interpreting the final results.

This WP encompasses writing the results in the required format (e.g., report, presentation, manuscript, or poster), any external communication regarding the project as well as the dissemination of results to both scientific and lay audiences. E-CORE-related communication such as website set-up or press releases will be also handled by WP 6. WP 6 also deals with registration in ENCePP and updating the entry when protocol and results reports are ready. It will liaise with SAB, data partners and Study Funder on study specific communication.

The existence of this WP does not preclude any partner from communicating E-CORE related activities, however, for these E-CORE approvals must be obtained prior to publishing results independently.

5.2 Enrolling new partners in the E-CORE Network

To identify data sources appropriate to be included in E-CORE, data from two extensive existing networks will be assessed: OHDSI and EHDEN, which include European data from both primary and secondary care settings. These networks are constantly developing, and large investments are being made to add data sources and foster collaboration. Any data asset can participate in E-CORE, provided it has already mapped its data to the OMOP CDM.

Data partners wishing to contribute must undergo a process of engagement in the network and quality check of the converted database. The criteria for a data source to be admissible into E-CORE consist of six domains, see Appendix 2. These criteria are not related to a specific study protocol, and not all databases will be deemed suitable for all protocols, however as a minimum, the data source must contain sufficient COVID-19 patients in either in-patient or ambulatory settings and 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). These criteria are checked through a special feasibility package run at the data partner and the results are loaded into the special E-CORE ShinyApp at https://dqdashboard.iqvia.com/ema_report1.

5.3 Data ownership and access, including data use limitations and data retention

E-CORE operations a federated (distributed) access model. Data partners remain in full control of their institutional data, both raw and in the OMOP CDM. It is the responsibility of the SAB to liaise with data partners to ensure protocols are filed with the Ethic Committee and receive approval prior to executing study code and sharing results. There will be no transmission of patient-level data at any time during these analyses and no extraction of patient-level data performance. Only aggregate statistics will be

shared. Study results will be transmitted in compliance with all institution-approved security protocols for transferring data such as secure file transfer servers with public-private key pairs.

To conduct the study code, each data partner executes a R package against their database to generate the results. After a review of these results, the data partner then returns them to the Study Coordinating Centre.

Archiving and Data retention

The final study protocol and amendments, the final statistical report, statistical programs and output files as well as the study aggregated results sets (interim and final) will be archived on a specific and secured drive centrally at the Study Coordinating Centre. The statistical programs will also be shared on GitHub. The quality control (QC) documentation generated by the individual data partner and shared with the Study Coordinating Centre, where it also gets archived.

All documents and aggregated result sets related to the conduct of a study will be retained for a period of five years in accordance with Good Pharmacoepidemiology Practice (GPP) guidelines. Longer archival of regulated documents about a specific pharmaceutical product is the responsibility of the funder or Market Authorisation Holder, which is typically as long as the product is authorised or for at least 10 years after the marketing authorisation has expired. If the Study Funder requires these documents to be retained by E-CORE for a longer period, the Study Coordinating Centre needs to be informed and an agreement between study partners is required. It is the responsibility of the Lead Investigator and all partners to inform the other investigators and institutions as to when these documents no longer need to be retained.

5.4 Standardizing databases to the OMOP CDM

To assess and analyse multiple data sources in a distributed or federated network, the data need to be harmonised into a common data standard. This standard is provided by a CDM. The CDM, combined with its standardised content ensures that research methods can be systematically applied to any data partner producing correct, meaningful, comparable and reproducible results.

All databases included in this network will be standardised to the OMOP CDM. This CDM covers the specification for all variables and its content that can be collected during the study. The OMOP CDM is developed and maintained by the OHDSI initiative and is described in detail at https://ohdsi.github.io/CommonDataModel/ and in The Book of OHDSI: http://book.ohdsi.org.

An overview of all the tables in the CDM is provided in Figure 2.

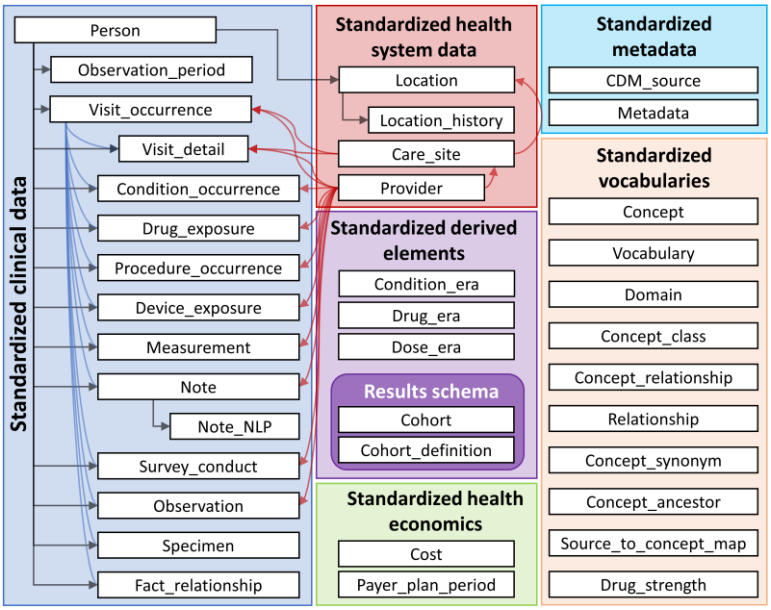

Figure 2. Overview of all tables in the CDM version 5.3

5.5 Privacy and security

Protection of patient privacy and general data security regulations is the responsibility of the data partners (Gini et al. 2020). E-CORE obligates each data partner to abide by the local and EU-wide data privacy rules and regulations.

The general privacy rules at each stakeholder level are provided below:

All levels

- Only the required personnel will have access to the data or study documents, which are to be stored in a secure environment.

At data provider level

- Each data provider is responsible for data access (privacy by design). Local rules apply.
- Person-level data is not shared across data partners or with the Study Coordinating Centre, only aggregated data are shared.
- Study packages will contain minimum cell count parameters to obscure any results which are derived from a selection falling below allowable reportable limits according to masking rules applicable for each contributing partner. It is responsibility of data partners to QC the results and mask the appropriate cells. Masked results are indicated with an asterisk.

At Study Coordinating Centre

- The R scripts created to perform the analysis are considered public information and are therefore shared on the Github platform.
- Other study documents are stored internally with restricted access to selected users and can be shared by email with the stakeholders, including the Study Funder.
- When the data partners report the aggregated results to the Study Coordinating Centre, this should be done with appropriate encryption.
- The protocol and study results will be made public, stored in the EUPAS register.

Section 6.0 The process of conducting a study in E-CORE

This section of Report No.2 is intended to be a practical guide to using the E-CORE framework for pharmacoepidemiological studies, describing how a Study Funder commissioning a study in the E-CORE network should engage. The following nine steps cover the all types of studies and not all are applicable for every study.

6.1 Defining the study question

- Once the need for an E-CORE study as emerged, the first step in the process is to clearly state the scientific question(s).
- If the Study Funder is not clear about the study question and needs help with defining it, the E-CORE network can be contacted and assist in this early stage

6.2 Contacting the network for a study proposal

- After the study question is clear, the Study Funder should contact the Administrative Centre with a study proposal including the scientific question and background, timeline and budget.
    - The Administrative Centre contact details are:

      IQVIA Solutions B.V.

      Herikerbergweg 314

      1101 CT Amsterdam

      the Netherlands

      Contact email: chris.vanbronckhorst@iqvia.com
- In order to assess whether or not the study is suitable for E-CORE, the Administrative Centre calls for an assessment meeting with the SAB and the data partners (Study triage meeting). During this meeting, the SAB will decide if the study will be conducted in the E-CORE or not and agrees on the Study Coordinating Centre, choosing from available centres.
- The Study Coordinating Centre has up to 4 weeks to come up with a proposal of the statement of work (SOW). The proposal does not involve a full protocol or detailed database feasibility and should be a minimal description of work activities associated with study execution, timelines, and deliverables.
- The Study Funder will evaluate the proposal and decide whether or not to go on with the study. On a case by case basis, during the evaluation period, there is possibility to amend the proposal, upon request from the Study Funder.
- The proposal is usually free of charge for the Study Funder, depending on the complexity.

6.3 Contracting

- If the proposal is accepted, a contract shall be signed between the Study Coordinating Centre (including naming of the principal Lead Investigator) and the Study Funder clearly defining the research project, budget, timelines, protocol agreement, study registration with regulatory

authorities, ethic committees and other bodies (as applicable by national law), data analysis and publication of study results.

- The Lead Investigator will always be a person without financial, commercial or institutional interests in any particular outcome of the study.

The following aspects should be addressed in the research contract:

- The procedure for achieving agreement on the study protocol.
- Adherence to the ENCePP Code of Conduct. The contract shall include the statement “The parties to this agreement and individuals acting on their behalf hereby commit to adhere to the rules of the ENCePP Code of Conduct in their entirety”. Or adherence to the ADVANCE Code of Conduct for collaborative vaccine studies.
- The main objectives and a brief description of the intended methods of the research that is the subject of the contract. Additional analysis requested by the Study Funder after contract signing will require a separate change order.
- The name of the study and a clear assignment of tasks and responsibilities of the core team members involved in the design and conduct of the study.
- The procedure for achieving agreement on the study protocol (number of iterations and reviews) as well as any involvement of the Study Funder in the development of the protocol.
- The total budget and the payment scheme. An indicative of costs for different study types is presented in Appendix 3.
- Intellectual property rights arising from the study and access to study data.
- A communication strategy for the scheduled interim (if applicable) and final results including relevant milestones.

A model for the contract between the Study Coordinating Centre and the potential Study Funder is attached in Appendix 4. The main elements are financials, terms and conditions, deliverables and timelines.

6.4 Set-up of the study team

The Study Coordinating Centre will invite partners to collaborate and will allocate resources needed for the study at hand. The budget will be also drafted and split accordingly. Regarding the study conduct, if the Study Coordinating Centre wants to be involved and has the necessary resources it can conduct most of the delivery itself, or optionally can assign the tasks to other partners.

6.5 Identifying available data sources

As early as during the proposal stage, the Study Coordinating Centre may consider existing data partners in the Network as well as engaging new partners if possible, if the study timeframe permits.

The partners have an opt-in option to participate in a specific study and participating in the network does not automatically involve participation in every study. They should have adequate data to respond to the research question, contain the desired population and sufficient follow-up time.

The data partners will advise if their own database is fit for purpose. Feasibility checks will be used to help decide at the proposal stage.

6.6 Study protocol and the statistical analysis plan

- Any study run in the E-CORE network can use the available protocol template (Deliverable No. 4) as a basis. This template can be used by external parties as well if they consider it appropriate.
- The protocol will be developed before the study commences, taking into account the elements of the ENCePP Checklist for Study Protocols and the study synopsis elements agreed in the proposal.
- The protocol must be designed to ensure that scientifically valid and sound results are generated independently from any potential conflicting interest of the funder or the researcher.
- The Lead Investigator shall have the final responsibility for its content, including protocol amendments.
- Feasibility studies that were carried out in advance, should be kept to a minimum, described in the protocol and shall not include pre-analyses of data.
- Any amendments or updates to the protocol after the study start should be documented in a traceable and auditable way including the dates of the changes.
- The protocol and the statistical analysis plan (SAP) contained therein or defined in a separate document will be subsequently registered in the EU PAS Register hosted by ENCePP, inclusive of adhering to the ENCePP Checklist for Study Protocol.
- Updates to the study protocol or the SAP in case of substantial amendments, progress reports where applicable, and study reports will also be entered in the EU PAS Register.
- The responsibility for the study record in the EU PAS Register shall ultimately lie with the Lead Investigator.
- The SAP is developed as a second step after the protocol and is usually not a deliverable to the Study Funder unless agreed upon in the study contract. The objective of this document is to help translation from the protocol into the programming and ensure reproducibility of the study.
- Any deviations from the analysis plan after finalisation of the protocol shall be clearly documented and a reasonable scientific explanation should be provided in line with the provisions for changes to the study protocol.
- Outcomes resulting from changes to the SAP after data analysis has begun, e.g. formation of new sub-groups based on knowledge of (initial) study results, may not be used for the purpose of verifying or rejecting the prior hypotheses of causal association stated in the protocol, but can be used to generate further hypotheses and in the interpretation of the results.

6.7 Ethics and data protection

Participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this

personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All the databases used in this study are already used for pharmacoepidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. The data partners are in responsible for the ethics application.

The use of the OMOP CDM and OHDSI tools will enable the federated analysis of these different databases without changing access rights to patient-level data. Each data partner is required to provide statement about Ethic Committee approval or exemption to participate.

6.8 Study execution

This step consists of creating and running the analytical programme, based on the protocol and SAP designed in earlier steps, QC of the programming and running the programme in the data partners. A dedicated team of statisticians and programmers will be assigned, usually part of the Study Coordinating Centre. After running the programme in their own database, data partners send interim and final results to the coordinating centre. After the final results are received, the reporting phase can begin.

The network will largely make use of common analytics distributed by OHDSI. Bespoke coding if needed will be created.

In terms of programming, all the analytical code and associated documentation will be publicly available on GitHub: https://ohdsi.github.io/DataQualityDashboard/articles/CheckTypeDescriptions and will reuse already existing packages as much as possible in order to increase both efficiency and validity of programming and study execution.

In terms of testing and validation of the code, the following are in place:

- The analytical code for the study is rigorously tested through automation of unit tests and is tested before distribution on real data available in house at the Study Coordinating Centre. If the coordinating centre does not have access to the data, the testing will be done in collaboration with the data partner.
- E-CORE studies packages contain analytical components that have been tested by the OHDSI community and are monitored by the core developers. This includes continuous integration of unit testing, regression testing, acceptance testing.
- Finally, the packages are tested by the partners on their own data and they are invited to report back any issues (user testing) which are then investigated and resolved.
- All the testing mechanisms are in place in a centralised testing environment by OHDSI
- The packages are publicly available on GitHub under an open source license.

6.9 Publication and reporting of study results

Communication(s) will be of a scientific nature (e.g. scientific journals, presentations at conferences,) and will be performed in collaboration with the sponsor. The aim of these studies is to be made available as soon as possible in order to support treatment decisions in the global COVID-19 pandemic.

Any authorship or publication plans will be discussed and agreed with the sponsor but may involve scientific journals, presentations at conference.

Dissemination and communication strategy for the study results should be pre-defined in the contract.

A clear summary of the main results of the study, whether positive or negative shall always be made available to the public according to the timetable agreed in the research contract or as specified in the study protocol.

Usually, the results for each country and database will be presented separately and meta-analyses, if necessary. At no point will there be pooling of any patient-level OMOP CDM data.

Study packages will contain minimum cell count parameters to obscure any cells which fall below allowable reportable limits. All study reports are designed to report out aggregate data only and will not identify individual patients or physicians.

The study results will be presented in an objective and truthful manner providing a comprehensive and accurate description of the findings. The report will follow the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society of Pharmacoepidemiology (ISPE) and the STROBE6 and RECORD statements, and also the Good Pharmacovigilance Practices (GVP) template for study reports.

The SAB will review any study results and publication and the Lead Investigator should either revise the results and publications or provide a rationale as to why the original version should be retained.

In line with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors (ICMJE), the authors of the study publication(s) should be those individuals who have made substantial intellectual contributions to the research, with authorship of each individual defined by the authorship criteria8 recommended by ICMJE. Information on the actual role of all authors and the Study Funder shall be provided. In addition, affiliations and conflicts of interest shall be disclosed. The lead author shall accept responsibility for the overall content of the study publication and the accuracy and integrity of the data presented as well as for any conclusions drawn from the data.

For studies that are (fully or partially) financed from external sources, the Lead Investigator shall always have the right to independently prepare publications of the study results irrespective of data ownership.

E-CORE is currently exploring the opportunity of having a dedicated website to communicate the network and its' offerings to a wider audience. We are also actively communicating the activities of E-CORE and we will invite potential interested funders to utilise this network for COVID-19 research.

Section 7.0 Sustainability of the Network

The E-CORE network is a publicly/private funded project, started and initially funded by EMA, and which, after June 2021 will accept both public and private funding.

For EU projects, a project is considered sustainable when the perceived return on investment is sufficient to attract relevant stakeholders to remain committed to support the project such that it has the required resources to continue to deliver projects for an extended period after the EMA financial assistance has been terminated.

The aim is for E-CORE to have a medium to long term sustainability of approximately 3 to 5 years if sufficient funding is secured. These can be achieved through the following mechanisms:

- Commercial partners will be invited to use the network for COVID-19-related research.

- Study Funders from both the public as well as the private sector will be accepted.

Section 8.0 Overview of current data partners

As detailed in Report No.1, the timing for data updates and lag time between updates and access for the current thirteen E-CORE network members are presented in Table 1.

Table 1. Update frequency and data latency of databases

Database	Update frequency	Data latency
LPD Belgium	6-monthly	6-8 weeks lag
LPD France	6-monthly	3 weeks lag
DA Germany	6-monthly	6 weeks lag
UK IMRD	6-monthly	6 weeks lag
LPD Italy	3-monthly	6 weeks lag
IPCI	6-monthly	3 months lag
SIDIAP	6-monthly	2-3 months lag
HM Hospitales	No update	No update
Serbia Clinerion	Daily	6-8 weeks lag
Health Informatics Centre	2-monthly	6-8 weeks lag
APHM France	Source data updated daily	3-months lag
Hospital del Mar	4-monthly	6 weeks lag
Technical University of Dresden	6-monthly	6 weeks lag

A questionnaire was filled out about any access restrictions to the data and ethics approvals manually. Results are shown in the table below.

Table 2. Access restrictions and ethics approval

	LPD Belgium	LPD France	DA Germany	IMRD UK	LPD Italy	IPCI Netherlands	SIDIAP	HM Hospitales	Serbia Clinerion	Health Informatics Centre	APHM France	Hospital del Mar	Technical University of Dresden
Contact of responsible person regarding legal aspects	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓
Contact of responsible person regarding privacy aspects of the data	✓	✓	✓	✓	✓	✓	✓	x	x	✓	✓	✓	✓
Ethics Committee process	No IRB process	No IRB process	No IRB process	6 weeks	No IRB process	Max 1 month, however the IRB meets only 2-4 times a year.	2-3 months	No IRB process	Max 2 months, as they meet once a month	No IRB process	No IRB process	2-3 months	6 weeks
Accept central IRB or require local sign-off	Local sign off	Local sign off	Local sign off	Local sign off	Local sign off	Central IRB not accepted	All projects are reviewed by a Scientific Committee before sending to an Ethics Committee.	Local sign off	Central IRB/ethical board exists, and if its' consent is required, then the consent from the University Clinical Center of	Local sign off	Local sign off (Health Data Access Committee: 1 meeting by month)	Local sign off	Local sign off

	LPD Belgium	LPD France	DA Germany	IMRD UK	LPD Italy	IPCI Netherlands	SIDIAP	HM Hospitales	Serbia Clinerion	Health Informatics Centre	APHM France	Hospital del Mar	Technical University of Dresden
									Serbia IRB is not required				
Additional ethics review	x	x	x	x	x	✓	✓	x	x	x	x	✓	x (if local ethics committee approval is done, then no additional review is needed)

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Appendix 1 The criteria for accepting a study/project within E-CORE network

E-CORE data can only be used for protocol based medical research studies that will ultimately promote public health. E-CORE will not accept any marketing studies.

Both private and public funding will be accepted.

For each study, there may be data source restrictions and so, not all data partners may be able to participate in each study. There will be an opt-out clause for data partners that do not wish to take part.

Type of observational studies that could be conducted if the data is fit for purpose and as long as they have a scientific objective and promote public health. The accepted studies fall broadly into the following categories, but these are not restricted:

- Pharmacovigilance studies: signal generation and rapid signal evaluation in electronic healthcare records, calculation of incidence rates of AEs to contextualize adverse events
- Incidence and prevalence studies – calculation of incidence and prevalence rates of outcomes in various populations.
- Safety and effectiveness of medicines/vaccines: assessing safety and/or effectiveness of licensed medicines/vaccines by following patients over time and comparing the drug of interest with an adequate comparator.
- Drug utilisation studies: Monitoring of uptake and appropriate use of drugs e.g. against HTA/regulator recommendations
- Impact assessment: measuring the impact of pharmacovigilance activities on processes of healthcare delivery, such as healthcare outcomes or drug utilisation patterns following changes to the product information. In addition, measuring dissemination of risk minimisation is of importance as well as changes in knowledge, awareness and behaviour of healthcare professionals and patients.

Appendix 2 The criteria for admitting a database in the E-CORE network

The criteria for admitting a database in the E-CORE network are based on a combination of: recommendations from (Hall et al. 2012), OMOP Data Quality Checks and published literature specific to COVID-19 research.

Data structure

- Population covered: The data source includes a sufficient population in terms of size, coverage and representativeness of country of origin
- Data update: The database is updated sufficient times (at least 6-monthly)
- Ability to link at least outcomes and drug exposure and, optionally laboratory values at patient level.

Longitudinal dimension

- Follow-up time: start and end of follow-up can be identified or inferred
- The average patient follow-up is long enough to allow meaningful research. This might differ from one study to another.
- Continuous and consistent data capture: No major breaks or changes in data collection over time for either individual patients or the whole population during the study observation period.

COVID-19 testing or diagnosis

- The database contains or will contain in the near future (for lagged data) a large enough COVID-19 patients' cohort either in primary or secondary care
- Diagnosis codes or laboratory tests that would allow identification of COVID-19 are captured
- Socio-demographic variables are captured
- Co-morbidities (any) are captured
- Drug treatments (any) are captured

Quality and validation procedures

- On the source data:
  - Data is entered by trained personnel
  - Appropriate general quality checks are routinely completed
- During extraction–transformation-load process
  - During this process several quality checks of the data are performed. The checks are on conformance, completeness and plausibility of values and are performed on relational, temporal and numerical values.
  - A Data Quality Dashboard (DQD) will be created for each database

- All issues found have to be solved or considered non-essential before the data can be used.
- Deviations are documented.

Privacy and security

- Compliance with privacy and security policy: All relevant local, regional and national policies been complied with
- No use of identifying information: All direct identifiers are removed or masked.
- No patient-level data are shared outside the site.

Access, Contracting & Ethics

- Willingness to participate and have resources available for transformation into CDM and running studies
- Allows collaboration with third party researchers as EMA
- The access model allows the OMOP conversion and a distributed network access
- An ethics and/or scientific review process in place for the study protocols

Optional: Previous involvement in research and database expertise

- Expertise required to use the resource available is available in house or externally

Appendix 3 Standard price list for studies in the E-CORE network

The following contains the recommended price structure. Individual studies will be negotiated and can deviate from these prices.

Types of analyses/studies possible in E-CORE

LOW — Complexity scale — HIGH

	Feasibility I	Feasibility II	Cohort I	Cohort II	Study
	Executed as rapid queries		Descriptive statistics	Protocol-driven analytics – **see types of studies relevant for E CORE in Appendix 1**	

Description	▪ Overall high level counts of a simple patient cohort
	▪ Usually 1 variable/parameter
	  • Drug usage
	  • Condition occurrence
	  • Demographic
	▪ Only readily accessible assets at the study coordinating centre
	▪ Query creation only in ATLAS
	▪ Reporting only counts
		▪ Overall high level counts of a more complex patient cohort
		▪ Multiple variables/parameters
		  • Drug usage
		  • Condition occurrence
		  • Procedures
		  • Lab tests
		  • Demographics
		  • Visits
		  • Providers
		▪ Any internal and external assets
		▪ Query creation in ATLAS or manually
		▪ Reporting counts and age/gender
			▪ Generate one cohort based on potentially complex set of inclusion and exclusion criteria
			▪ Report on patient characteristics:
			  • Gender
			  • Age
			  • Con/medication
			  • Comorbidities
			  • Top Procedures
			  • Cost
			  • Follow-up time
			▪ Incidence/Prevalence Rates
			▪ Exposure Rates
			▪ Report tables and graphs
				▪ Participate in one-iteration protocol definition with study requester
				▪ Generate multiple parallel related complex cohorts
				▪ Calculate treatment patterns and pathways
				▪ Calculate outcomes (OS, PFS, EFS, response ratios)
				▪ Calculate adherence and persistence
				▪ Create healthcare resource utilization report
				▪ Summarize in high-quality report
					▪ Participate in multiple iterations of protocol definition with study requester
					▪ Define and generate complex test, comparator and outcome cohorts
					▪ Develop positive and negative controls
					▪ Define study design and analytical parameters
					▪ Build population-based estimation (pharmacoepi) study
					▪ Build patient level prediction (probabilistic model) study
					▪ Summarize in publishable manuscript

Examples	What is the total number of patients with Prurigo Nodularis in 2018?	What is the count of low-dose aspirin (75mg-100mg) in primary and secondary cardiovascular prevention patients only in countries where cardio-aspirin is prescribed?	Among patients with psoriasis over last 5 years, how many presented with cardiovascular diseases and which ones?	Among patients with pneumonia how quickly do they develop ocular retinopathy within two years?	Evaluate the risk of Major Adverse Cardiovascular Events (MACE) in patients with psoriasis treated with Adalimumab compared to topical corticosteroids over last 5 years.

*Manual query means bespoke programming in R.

Type of design	1 database	2 databases	3 databases	4 databases	5 databases	6 databases	7 databases
Feasibility I	1,800	2,600	3,400	4,200	5,000	5,800	6,600
Feasibility II	7,510	10,020	12,530	15,040	17,550	20,060	22,570
Cohort I	39,000	54,000	69,000	84,000	99,000	114,000	129,000
Cohort II	96,400	136,800	177,200	217,600	258,000	298,400	338,800
Study - see types of studies relevant for E-CORE in Appendix 1	146,000	206,000	266,000	326,000	386,000	446,000	506,000

Prices are in Euros, valid at 12th April 2021

These costs are indicative and valid only for standard study types and any additional analysis/objective/cohort requested will be charged extra. The costs do not apply to PASS studies for which multiple iterations of the protocols and complex analysis are usually required. Different databases might charge different prices.

Appendix 4 Model for the contract between the Study Coordinating Centre and the potential Study Funder

This Agreement ("Agreement") for services is effective as of **[date]** by and between [**Study coordinator legal entity name and address]** ("IQVIA"). an organisation organised under the laws of [**insert relevant jurisdiction**], and [***INSERT NAME OF INDIVIDUAL]*** of [***ADDRESS***] ("Study Funder").

WHEREAS, Study coordinator wishes to obtain from Consultant the services described in the attached Exhibit A and Consultant desires to provide such services to IQVIA in accordance with the terms of this Agreement.

NOW, THEREFORE, in consideration of the foregoing and the mutual promises and covenants contained below, the parties agree as follows:

1. **Services**

a. IQVIA hereby retains and Consultant hereby agrees to provide those services described in Exhibit A attached, and such other services as IQVIA and Consultant may expressly agree upon in writing from time to time ("Services"). Services shall be rendered at Consultant's principal place of business or at such other places, and at such times, as IQVIA may request. In addition, Consultant shall adhere to IQVIA Supplier Code of Conduct, a copy of which is available at: https://www.iqvia.com/about-us/suppliers and agrees to comply with the Anti-Corruption Provisions in Exhibit B and all other provisions set out in any other Exhibits and Appendices to this Agreement.

b. All Services performed by Consultant shall be of the highest professional standards and performed to IQVIA's reasonable satisfaction.

2. **Remuneration**

a. IQVIA shall pay Consultant during the term of this Agreement for Services rendered in accordance with Exhibit A attached.

b. Consultant acknowledges and agrees that he is an independent contractor and IQVIA shall have no obligation to provide compensation, insurance, expense reimbursements or other similar benefits to Consultant except as described in Exhibit A.

c. In accordance with the IQVIA Travel and Expense Policy, IQVIA shall pay travel expenses incurred by Consultant in connection with performing the Services; provided, however, no such expenses shall be paid by IQVIA unless the incurring of such by Consultant has received the prior written approval of IQVIA. In order to be reimbursed, all expenses must be supported by receipts.

3. **Term and Termination**

a. The term of this Agreement shall be for a period:
beginning on: date, and
ending on: date.

b. Either party may terminate this Agreement at any time, with or without cause, upon thirty (30) days' advance written notice to the other party. In the event this Agreement expires or is terminated for any reason, any provision of this Agreement that expressly or by implication is intended to come into or continue in force on or after expiry or termination of this Agreement including paragraphs 5, 6 and 8, 10 and paragraphs 12 (a), (b), (c), (e) (g) and (h) of this Agreement shall remain in full force and effect.

IQVIA may at any time terminate this Agreement with immediate effect with no liability to make any further payment to Consultant (other than in respect of any accrued fees or expenses at the date of termination) if:

(i) Consultant is in material breach of any of its obligations under this Agreement;
(ii) The provisions of Exhibit B, Section 11 apply; or
(iii) in the event of insolvency of Consultant.

c. Any delay by IQVIA in exercising its rights to terminate shall not constitute a waiver of those rights.

d. Neither party hereto shall be obligated to enter into any renewal or extension of this Agreement except upon such terms and conditions as shall be mutually agreeable to IQVIA and Consultant, all as shall be fully set forth in a formal written document signed by the parties hereto.

e. No termination pursuant to this Agreement shall impair the right of Consultant to be remunerated for work completed and accepted in writing by IQVIA prior to the date of termination and expressly compensable under the terms of this Agreement.

4. **Limitation of Authority**

Consultant is engaged by IQVIA only for the purposes and to the extent set forth in this Agreement. The relationship of Consultant to IQVIA is that of independent contractor. Neither party shall represent that it has any authority to assume or create any obligation, express or implied, on behalf of the other party, or to represent the other party as agent, employee, or in any other capacity, except as specifically provided in this Agreement.

5. **Confidential Information**

a. "Intellectual Property" means:

(i) patents, trademarks, registered designs, applications for any of those rights, trade and business names, unregistered trademarks, copyrights, know how rights in designs and inventions and database rights.

(ii) rights under licenses, consents, orders, statutes or otherwise in relation to rights in paragraph (i); and

(iii) rights of the same or similar effect or nature as those in paragraphs (i) and (ii),

in each case in any jurisdiction.

b. "Information" means ideas, concepts, inventions, know-how, techniques, strategies, trade se-

crets, collections of data, surveys, identification of problems or solutions, identification of business opportunities and all memoranda, minutes, letters, software, drawings, reports, materials protected by Intellectual Property rights and all other kinds of documents, recordings, and copies (in whatever form or media) containing or reflecting such information.

c. "IQVIA Confidential Information" means:

(i) all Information communicated by IQVIA to Consultant (whether before or after the signing of this Agreement); and

(ii) all Information created, developed or collected by Consultant, whether solely or jointly with others (whether before or after the signing of this Agreement or before or after Consultant ceases to provide Services to IQVIA), as a result of providing Services to IQVIA or as a result of receiving or using the Information; provided, however, that this paragraph 5 will not apply to any Information Consultant obtains independently of Information communicated by IQVIA to Consultant and independently of Services provided to IQVIA.

d. Consultant shall hold all IQVIA Confidential Information in strictest confidence, in any event not employing less than reasonable means to protect the confidence of this Confidential Information. Consultant agrees not to disclose IQVIA Confidential Information to any third party, whether before, during, or after the term of this Agreement, without the prior express written approval of an authorised representative of IQVIA. Consultant shall not use IQVIA Confidential Information for Consultant's own account or business. Upon conclusion of the Services provided to IQVIA, Consultant shall promptly return to IQVIA all documents, copies or other recordings containing or reflecting IQVIA Confidential Information.

6. Ownership of IQVIA Confidential Information

a. All Intellectual Property rights in IQVIA Confidential Information are, or shall become upon their creation, the property of IQVIA for its sole and exclusive use, benefit, and assignment. Consultant hereby assigns by way of future assignment all Intellectual Property rights in IQVIA Confidential Information to IQVIA immediately on their coming into existence.

b. Consultant shall promptly disclose to IQVIA all information, data and materials (the "Materials") obtained by him in the course of performing Services under this Agreement as well as all IQVIA Confidential Information not received directly from IQVIA. Consultant hereby transfers, conveys, and assigns all title to the media on which the Materials subsist and any of Consultant's Intellectual Property rights in the Materials and IQVIA Confidential Information to IQVIA.

c. To the extent that full legal title to any Intellectual Property rights so arising shall fail automatically to belong to IQVIA, Consultant shall hold such rights in trust for IQVIA absolutely and will provide to IQVIA at IQVIA's expense any lawful assistance to file for protection of, register, assign or otherwise further perfect IQVIA's ownership of such Intellectual Property rights.

d. It is agreed and understood by both parties that IQVIA is expressly entitled to use Consultant's name in connection with any written materials or Services with which Consultant has been associated.

e. Consultant shall, to the fullest extent permitted by law, waive all moral rights in IQVIA Confidential Information.

7. Data Protection

a. In this paragraph 7 and in any applicable Exhibits and Appendices, the terms "Personal Data", "Data Controller", "Processor" and "Processing" are as defined in applicable national legislation, including, as from 25 May 2018, the 'EU Regulation 2016/679 on the protection of natural persons with regard to the processing of Personal Data and on the free movement of such data' ("GDPR").

b. Pursuant to this Agreement and in addition to such other data protection obligations (if any) set out in any Exhibits hereto, the Consultant will provide to IQVIA Personal Data. The Personal Data will consist of information about the Consultant. This Personal Data will be processed by IQVIA to administer the Agreement with the Consultant, to facilitate communication between parties to the Agreement and to compensate the Consultant for the Services rendered. The Personal Data will not be disclosed to any person outside the IQVIA group of companies (being IQVIA or any of its Affiliates) ("IQVIA Group of Companies"), unless required by law. The Personal Data will be kept secure and confidential, but may be transferred for the purposes outlined in this paragraph 7 to countries outside the European Economic Area, including the United States, which may not have in place protections for Personal Data considered 'adequate' by the European Commission.

c. Pursuant to this Agreement the Consultant may gain access to Personal Data held by IQVIA. In handling and Processing this Personal Data the Consultant agrees to abide by IQVIA company policy on data protection and undertake any training on data protection at the request of IQVIA.

d. For the purposes of this clause, "Affiliate" shall mean any entity which from time to time is directly or indirectly Controlled by IQVIA, any entity which from time to time is directly or indirectly Controlling IQVIA, and any entity which, directly or indirectly, is under common Control with IQVIA, and "Control" shall mean in relation to a body corporate, the power of a person to secure that the affairs of the body corporate are conducted in accordance with the wishes of that person: (i) by means of the holding of shares, or the possession of voting power, in or in relation to that or any other body corporate; or (ii) as a result of any powers conferred by the articles of association or any other document regulating that or any other body corporate, and "Controlled" and "Controlling" shall be construed accordingly.

8. Representations

Consultant agrees and shall perform the Services in compliance with all applicable laws, rules, and regulations, and in conformance with the professional standards applicable in Consultant's industry and any applicable good clinical practices, guidelines and standard operating procedures. If the Services are to be performed pursuant to a protocol, Consultant will strictly follow all terms and provisions of the protocol. Consultant warrants that he has never been debarred under 21 U.S.C. Section 335a or convicted of a crime relating to the manufacture or testing of drugs, pharmaceutical products, or medical devices. Consultant will promptly notify IQVIA if, during the course of the Services, Consultant is under investigation for such a crime or debarment. Consultant warrants that neither this Agreement nor the provision of Services will violate any other agreement or obligation of Consultant.

9. Taxes and Insurance

a. The Consultant shall be solely responsible for and shall account for all taxes, charges and levies of any description including income tax and value added tax and social security contributions to the appropriate authorities.

b. If IQVIA is found liable or liable to account for any tax of any description (including any National Insurance contributions, social security contributions and income tax) in respect of any payment made to the Consultant hereunder, the Consultant will indemnify IQVIA on demand such amount as is necessary to put IQVIA in the same net of tax position as it would have been if it had not been liable or liable to account for such tax, National Insurance, social security, liabilities, deductions, contributions, assessments or claims (including all reasonable costs, expenses and any penalty, fine or interest incurred or payable by IQVIA in connection with or in consequence of any such liability, deduction, contribution, assessment or claim), where such recovery is not prohibited by law.

c. The Consultant shall take out and maintain in force all appropriate insurance policies.

10. Assignment

Consultant shall not assign, transfer, or delegate any of Consultant's rights or obligations under this Agreement without the prior written permission of IQVIA. Any attempt by Consultant to assign, transfer or delegate any of its rights or obligations under this Agreement without such permission shall be void. IQVIA may assign, transfer, or delegate its rights or obligations under this Agreement to any company within the IQVIA Group of Companies (as defined in paragraph 7 b).

11. Miscellaneous

a. All notices or other communications in connection with this Agreement shall be made in writing and delivered personally or sent by prepaid certified or registered mail, with return receipt requested, or sent by overnight courier (e.g. Federal Express or DHL), addressed to the other party at the address specified at the beginning of this Agreement or at such other address as may have been furnished in writing. Notice shall be deemed to have been duly made or given upon receipt by the party to whom such notice or other communication is sent.

b. This Agreement and any dispute or claim arising out of or in connection with it or its subject matter or formation (including non-contractual disputes or claims) shall be governed by and construed in accordance with English law. The parties irrevocably agree that the courts of England shall have exclusive jurisdiction to settle any dispute or claim that arises out of or in connection with this Agreement or its subject matter or formation (including non-contractual disputes or claims).

c. Failing to enforce the provisions of this Agreement or to require the other party to perform any of the provisions of it shall not be construed to be a waiver of such provisions; nor will it affect the right of either party to subsequently enforce any provision of this Agreement.

d. No modifications, amendments or waiver of any of the provisions of this Agreement shall be binding upon the parties unless made in writing and duly executed by Consultant and an authorised representative of IQVIA.

e. The headings of the paragraphs in this Agreement are used for convenience only and shall not affect the meaning or interpretation of the content.

f. This Agreement may be signed in one or more counterparts, all of which taken together shall constitute one and the same agreement.

g. A person who is not a party to this Agreement shall not have any rights under the Contracts (Rights of Third Parties) Act 1999 to enforce any term of this Agreement. The rights of the parties to terminate, rescind or agree any variation, waiver or settlement under this Agreement are not subject to the consent of any other person.

h. This Agreement and the exhibits and appendices attached set forth the entire agreement between the parties and supersedes prior proposals, agreements and representations related to the subject matter of this Agreement, whether written or oral. Terms or conditions different from or in addition to those in this Agreement, including any contained in any purchase order or acknowledgment form from Consultant, shall not be binding on IQVIA unless specifically agreed to in writing by an authorised representative of IQVIA. In the event of any inconsistency between this Agreement and Exhibit A, the terms of this Agreement shall prevail.

The terms and conditions of this Agreement are hereby acknowledged and accepted by each of the parties by the signature below of the Consultant and of a duly authorised representative of IQVIA.

[INSERT FULL NAME OF IQVIA LEGAL ENTITY]

[INSERT FULL NAME OF Study Funder]

By: _____

_____

Name: _____

Title: _____

EXHIBIT A

Services and Fees

DESCRIPTION OF SERVICES:

PROVIDE FULL DETAILS OF SERVICES TO BE PROVIDED BY CONSULTANT TO IQVIA

[Detailed Description of milestone/services to be set out here]

Consultant acknowledges and agrees that no additional work may be performed unless agreed to in writing in advance by an authorised representative of IQVIA. Upon the request of IQVIA, Consultant agrees to promptly provide IQVIA with a written report detailing Consultant's activities or proposed activities for the period of time requested.

FEES:

[Provide detail as to the fee rate, budget, and any special payment terms]

Any modification of the Fees must be agreed to in writing in advance by an authorised representative of IQVIA. Consultant shall invoice IQVIA on the following basis: **[insert invoice schedule].** IQVIA shall pay Consultant´s invoices within 60 days of receipt thereof.

EXHIBIT B

Anti-Corruption Provisions

1. **Compliance with Anti-Corruption Laws**.

a. The Consultant represents and warrants that he will take no action, directly or indirectly, that would constitute a violation of the United States Foreign Corrupt Practices Act of 1977, as amended from time to time (the "FCPA"), the United Kingdom Bribery Act 2010, as amended from time to time (UKBA), any other applicable anti-corruption laws or regulations, or IQVIA's Policy against Bribery and Corruption.

b. Specifically, the Consultant represents and warrants that in carrying out his responsibilities under this Agreement neither he, nor any other party acting on his behalf, will directly or indirectly make, offer, authorise, promise to make, or receive any Payment:

i. to obtain or retain any contract, business opportunity or other similar benefit;

1. to or for the use or benefit of any Government Official;
2. to any other person where the Consultant knows or has reason to know or suspect that any part of such Payment will be directly or indirectly given or paid by such other person, or will reimburse such other person, for any Payment previously made or given to any Government Official when such Payment could not be made directly in accordance with this Section 1; or
3. to any person where such Payment violates any laws, decrees, regulations or policies having the force of law in the country or countries of such person or applicable to such person or the laws of the United States of America and England and Wales.

ii. to or from any person, whether or not a Government Official,

1. with the intention to bring about or reward the improper performance of a duty or obligation to which the person is subject; or
2. with the knowledge or belief that the acceptance of the advantage in itself constitutes the improper performance of the person's duty or obligation.

c. Definitions. For the purposes of this Section 1, the following definitions shall apply:

i. The "Government" is any national, federal, state, provincial, municipal, local, or any other Government, including any department, agency, instrumentality, company, corporation, or other entity owned or controlled by any government;

ii. A "Government Official" is any

1. official, employee, or representative of any Government or state owned enterprise.
2. political party, or any Official, employee, or representative of any political party;
3. candidate for political office;
4. Official, employee, or representative of any international organisation.

iii. A "Payment" is any monetary payment, loan, donation, gift, in-kind service, or any other thing of value, or any financial or other advantage.

2. **Facilitating Payments**. Consultant shall not make Facilitating Payments. A Facilitating Pay-

ment is a small value payment made to a Government Official to expedite or secure the performance of routine, or non-discretionary Governmental action, which is ordinarily and commonly performed by a Government Official.

3. **No Anti-bribery Offences**. The Consultant represents and warrants that he has not been convicted of, pleaded guilty to, or charged with any offence involving fraud, corruption or bribery in any jurisdiction or country.

4. **Fully Qualified and Authorised**. The Consultant represents and warrants that he is fully qualified to assist IQVIA and is authorised to act in the capacity contemplated by the Agreement in accordance with all applicable laws. Further, the Consultant has complied with any applicable registration and licensing requirements.

5. **Immediate Disclosure by Consultant**. The Consultant agrees to immediately inform IQVIA if a possible violation by the **Consultant** of the FCPA, UKBA, other applicable anti-bribery law, and/or IQVIA's Supplier Code of Conduct including the anti-corruption provisions thereof has taken place. Further, if any Government Official or any relative of such Government Official solicits, asks for, or attempts to extort, any money or thing of value from the Consultant, the Consultant shall refuse such solicitation, request or extortionate demand, and immediately report the event to IQVIA.

6. **IQVIA's Right to Disclose**. The Consultant agrees that full disclosure of information relating to a possible violation by the Consultant of applicable law, including a violation of the FCPA, UKBA, or any other applicable anti-bribery law, may be made by IQVIA at any time and for any reason to the U.S. or UK Government, its agencies, and/or any other Government or non-Government party.

7. **Compliance Training**. The Consultant warrants that he fully understands these provisions relating to his business conduct and will comply with these provisions. The Consultant agrees to make himself available for compliance training as directed by IQVIA.

8. **Certification of Non-Violation**. If requested by IQVIA, the Consultant warrants that he will furnish IQVIA a signed non-violation certification on an annual basis.

9. **Records and Audit**. The Consultant shall keep accurate accounts, books, and records showing all costs and charges incurred in accordance with generally accepted accounting principles and practices. Such accounts and records shall be made available in the Consultant´s office during normal business hours for inspection by IQVIA or its designee. The Consultant shall preserve such accounts and records for at least five (5) years after the end of the term of this Agreement. IQVIA shall further have the right, upon reasonable written notice to the Consultant, to audit compliance by the Consultant with all provisions of this Agreement including, but not limited to, provisions of this Agreement related to compliance with the FCPA, UKBA, and any other applicable anti-bribery laws. The Consultant agrees to fully cooperate with respect to any such audit or other compliance review.

10. **Accuracy of Representations at All Times**. The Consultant undertakes that all of the listed Representations and Warranties will remain true, accurate, and complete at all relevant times.

11. **Termination**. At its sole discretion, upon notification to the Consultant, IQVIA may terminate this Agreement effective immediately if:
    a. IQVIA makes a good faith determination that the Consultant has breached these Representations and Warranties and/or otherwise has committed a violation of the FCPA, UKBA, and/or any other applicable anti-bribery laws; OR
    b. the Consultant fails or refuses to promptly furnish the anti-bribery non-violation certification referenced in Section 8 above.

EXHIBIT C

ADDITIONAL DATA PRIVACY OBLIGATIONS

Data Privacy

If in the performance of the Services the Consultant is required to process Personal Data on individuals on behalf of IQVIA, including without limitation for the purposes of conducting a market research survey, then the Consultant shall be bound, and shall procure that Personnel shall be bound, by the following provisions:

(i) IQVIA or the client of IQVIA is the Controller with respect to the Personal Data collected, in that IQVIA or the client of IQVIA determines the purposes and manner in which that Personal Data is collected and further processed. The Consultant is a Processor with respect to the Personal Data collected, in that the Consultant processes the Personal Data on behalf of IQVIA or the client of IQVIA. The Consultant shall only process this Personal Data under instruction from IQVIA in its capacity as Controller or as an agent of the client as Controller; and will at all times take all appropriate technical and organisational measures against unauthorised or unlawful Processing of Personal Data and against accidental loss or destruction of, or damage to, such Personal Data. The Consultant shall in particular ensure that Personal Data processed on portable media are encrypted. The Consultant agrees in particular (without limitation) that with effect from 25 May 2018, to the extent that Consultant processes Personal Data originating from the European Union on behalf of IQVIA under this Agreement, Consultant shall comply with its obligations as a Processor under the GDPR in full, and comply with the obligations on a Processor required to be incorporated into Processor agreements under Article 28 of the GDPR as if they were set out herein in full. If IQVIA or the client of IQVIA as Controller shall so request, Consultant will enter into a longer form agreement incorporating the provisions specified above. The details of the subject matter, nature, purpose and duration of the data processing and the type of Personal Data and categories of data subjects are set out in Appendix 1. IQVIA reserves the right to audit the Consultant's Processing of Personal Data under this Agreement.

(ii) To the extent that the Consultant sources the contact details of individuals in the performance of the Services, the Consultant will ensure that necessary consents have been obtained and notices provided to individuals.

(iii) The Consultant will provide information to any individual from whom Personal Data is obtained, which advises that person that their data is being collected on behalf of IQVIA or its clients for pharmaceutical market research purposes and that the data will only be released to its clients in anonymous or aggregate form.

(iv) The Consultant will notify IQVIA of any individual who objects to being contacted in accordance with this Agreement.

(v) All Personal Data collected shall be anonymised prior to transmission to IQVIA, including any nominative information contained within free text fields.

(vi) The Consultant is obliged to abide by the Market Research Society Guidelines.

(vii) Any third party contracted by the Consultant to assist in the performance of the Services shall be subject to the same terms on confidentiality and data protection as established in this Agreement.

EXHIBIT D

PHARMACOVIGILANCE OBLIGATIONS

1. Reporting Requirements

a. Where required by Applicable Law, Consultant shall collect any information in or coming into his possession or control in the performance of the Services hereunder in respect of any products specified by IQVIA, regardless of source, relating to an Adverse Event (AE), Special Situation, AE associated with a Product Quality Complaint (AEPQC), Undesirable Effect (UE) or Adverse Device Effect (ADE), as applicable and Incomplete Cases, in a format as specified by IQVIA.

b. Consultant shall (subject always to the Consultant's right under applicable law and regulation to disclose such information) forward to IQVIA such information immediately, but in no case later than the same day of him becoming aware of such information (i.e. the same day such information comes into his possession or control). For the avoidance of doubt, all Incomplete Cases should also be collected and forwarded to IQVIA within the same timescales.

c. Reporting criteria to IQVIA are met when an AE, Special Situation, AEPQC, UE, or ADE is linked to the Product, by a reporter in the context of a specific subject/patient. If details about the reporter and/or subject/patient details are not available, Consultant should forward the case regardless to IQVIA, i.e. the minimal information required for notification to IQVIA is a suspect Product and an event.

2. Training

The Consultant shall ensure he is trained in accordance with IQVIA's requirements in the collection and reporting of AEs, Special Situations, AEPQC, UEs or ADEs, prior to the start of any Services and at such other intervals as IQVIA may require.

3. Establishment of a Tracking System

a. The Consultant shall establish and maintain a tracking system for the collection, recording and collation of safety information as required herein.

b. Consultant must provide a summary table containing all identified AE, Special Situation, AEPQC, UE and ADE reports that have been reported during the Services as applicable, in the format and with the frequency required by IQVIA. Consultant shall address any query from IQVIA in respect of any inconsistent or unclear information set out in any report submitted within the same timelines and using the same mechanism as applicable to initial report.

4. Retention of records

Consultant shall maintain and archive records of all source documentation generated by the activity (records, questionnaires, reports), personnel training records, reports and other relevant information relating to the Services hereunder for at least five years or such longer period as is required by Applicable Law and/or as communicated by IQVIA to Consultant. Consultant must have appropriate storage capabilities (e.g., preventing accidental damage of physical records and appropriate back up

of electronic storage systems) if storing original AE, Special Situations, AEPQC, UE and ADE documentation. Notwithstanding the above, before Consultant destroys any safety records he will notify IQVIA of his intention to do so, affording IQVIA the opportunity to retain such records if it so wishes, subject always to the Consultant's right under applicable law and regulation to disclose such records.

5. Audit and Inspection

IQVIA and its clients reserve the right to audit the Consultant's pharmacovigilance obligations under this Agreement on reasonable notice and during normal business hours during the term of this Agreement and for two years thereafter, or such longer period as is communicated by IQVIA to the Consultant. If any governmental or regulatory authority inspects or audits Consultant's work or records relating to the Services, Consultant will immediately notify IQVIA and will provide copies to IQVIA of all relevant notices and correspondence to and from such authority. The Consultant agrees to fully cooperate with respect to any such audit or inspection.

6. Definitions used in this Exhibit

a. "**Adverse Event**" (**AE**) means any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

b. "**Adverse Device Effect**" (**ADE**) means an adverse event related to the use of a medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device. This also includes any event that is a result of a use error or intentional misuse.

c. "**Applicable Law**" means the applicable laws and regulations pertaining to pharmacovigilance including any pharmacovigilance requirements of any applicable Regulatory Authority in the relevant country [of the Territory.]

d. "**Incomplete Case**" means a reportable AE, Special Situation, AEPQC, UE or ADE case sent to Consultant which at a minimum contains a suspect medicinal product and a suspect event when reported by the Consultant to IQVIA i.e. information about the subject/patient and/or reporter are not contained in the report.

e. "**Product Quality Complaint**" (**PQC**) means any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a product after it is released for distribution.

f. "**Regulatory Authority**" means any applicable federal, national, regional, state, provincial or local regulatory agencies, departments, bureaus, commissions, councils or other government entities regulating or otherwise exercising pharmacovigilance authority with respect to any relevant product in the relevant territory.

g. "**Special Situation**" means occurrences or reports that may not contain an adverse event, which must still be collected and reported in order to meet regulatory safety reporting requirements:

- Overdose of relevant product,

- Pregnancy exposure (maternal and paternal),
- Exposure to the relevant product from breastfeeding,
- Suspected abuse / misuse of the relevant product,
- Inadvertent or accidental exposure to the relevant product (including occupational exposure),
- Any failure of expected pharmacological or medical device action (i.e. lack of effect) of the relevant product,
- Unexpected therapeutic or clinical benefit from use of the relevant product,
- Medication error involving relevant product with or without patient / consumer exposure to the relevant product, (e.g. name confusion) OR that caused an unintended effect or could cause an intended effect,
- Suspected transmission of an infectious agent via relevant product,
- Expired drug use and falsified medicine,
- Off-label use - situations where relevant product is intentionally used for a medical purpose not in accordance with the authorised product information

h. "**Undesirable Effect**" (**UE**) means an adverse reaction for human health attributable to the normal or reasonably foreseeable use of a cosmetic product.