REQUEST FOR PROPOSAL

COVID-19 VACCINE SAFETY SIGNAL DETECTION STUDY

November 2020

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1. Proposal Guidelines and Requirements

This is an open and competitive process. The issue of this document does not constitute an offer to trade and Service Provider is not bound to conduct business on the basis of any responses to the document. Any commercial arrangements are subject to contract.

Proposals received after 3rd December 2020 will not be considered and will be returned unopened, except if late return has been justified and accepted by the Vaccine manufacturers.

The members of the COVID-19 vaccine working group of Vaccines Europe are seeking to conduct COVID-19 vaccine post-authorization safety studies using common methodological approaches while allowing for brand-specific adaptations. This Request For Proposal (RFP) is issued by Vaccines Europe for this purpose. All information (including dates, numbers, and other figures) given in this RFP and any information delivered pursuant to this RFP is as accurate as possible at the time of preparation but may change in the future. All such information is provided for indicative purposes only so as to provide the potential Service Provider with an indication of the scope of requirements. It is the potential Service Provider's sole responsibility to undertake whatever investigation and due diligence it considers to be appropriate in order to verify the accuracy of any information provided to it through the RFP or otherwise.

The information provided in this and any subsequent related document is provided in strict commercial confidence. This also applies to all other communications between Vaccine Manufacturers and Service Providers. It must not be divulged to a third party without the prior express written consent of Vaccines Europe.

Your responses to the RFP will be shared and jointly reviewed by all Vaccine Manufacturers participating to the COVID-19 vaccine working group of Vaccines Europe. The Vaccine Manufacturers reserves the right in their absolute discretion to copy and distribute within its companies, its professional advisers, its auditors and its affiliates all or any part of the Service Provider's response document for the purposes of analysis and assessment. Submission of a response document shall be deemed as a grant to Vaccine Manufacturers of a right to copy such response document. Provisions of this RFP and the contents of the successful responses are considered available for inclusion in final contractual obligations. The price you quote should be inclusive. If your price excludes certain fees or charges, you must provide a detailed list of excluded fees with a complete explanation of the nature of those fees.

Potential contracts resulting from successful proposals will be made between the Service Provider and interested Vaccine Manufacturers on an individual basis. Every committed Vaccine Manufacturer will act as an individual sponsor to the study.

Every Vaccine Manufacturer reserves the right to accept other than the apparent lowest priced proposal and to accept or reject any proposal in whole or in part, or to reject all proposals. Specific evaluation information is not disclosed to any of the bidders. All decisions are final and may not be appealed. If no proposal is accepted, the vaccine manufacturers reserve the right to abandon the work or to have the work performed in such other manner as they may elect.

Every Vaccine Manufacturer cannot guarantee that all of its requirements will be satisfied as a result of this RFP and cannot offer exclusive rights to any selected Service Provider.

The Service Provider will be responsible for all costs and expenses it incurs (i) in providing responses to this RFP; (ii) in obtaining or providing any additional information required in order to facilitate the evaluation process; and (iii) in relation to any subsequent negotiations.

The reproduction of any part of this RFP by photographic, electronic or other means is permitted only for the sole purpose of preparing Service Provider's response to this RFP.

The Marketing Authorization Holder (MAH) is the sponsor of the study. Options to incorporate continuous input from expert scientists from MAHs, for example as member of the study team, should be described, as well as any specific code of conduct which would apply.

2. Structure and Contract Terms

The structure and contract terms will be decided as part of the proposal selection and contracting for any selected approach following this RFP, if applicable.

3. Description and Objectives

3.1. Purpose:

This request seeks proposals from selected service providers to design and conduct real-time monitoring of the occurrence of medically-attended adverse events following immunization (AEFI; including a predefined list of adverse events of special interest (AESI)) with COVID-19 vaccines (at brand-specific level) for the purpose of signal detection in the EU as soon as the vaccination starts. The proposed safety surveillance must fulfill the requirements of the EMA Core RMP guidance (not available yet).

3.2. Research objective:

The key objective is to rapidly detect a potential clinically significant change in the frequency and/or severity of medically-attended AEFI, including a predefined list of AESI following immunization with COVID-19 vaccines at the brand-specific level. The focus should be on signal detection in terms of frequency and/or severity of such events.

3.3. Methodology:

An active surveillance study (post authorization safety studies (PASS)) should be designed and put in place fulfilling the requirements as described in the EMA Core RMP guidance (not available yet). A proposal should be shared with Vaccines Europe.

The proposal should include a plan to develop a study protocol following the EMA PASS template, as well as a comprehensive study feasibility assessment considering the key following methodological aspects:

- The study should follow the GPP, GVP, and ENCePP methodological guidelines principles

- General and special populations: the capacity to enroll and follow-up subjects from the first priority group(s) (health care workers, …) for vaccination and other important special populations ((frail) elderly, immunocompromised, pregnant women), as well as relevant specific follow-up (such as pregnancy and newborn outcomes) should be assessed and be part of the proposal
- The data collection approach should allow the collection of COVID-19 specific risk factors such as smoking, a higher body mass index (obesity), older age, gender, post-menopausality, and pre-existing conditions (including hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, malignancy, chronic kidney disease, sickle cell disease, and weakened immune systems)
- The detection of AEFI/AESI should be (near-) real time to ensure rapid safety risk detection and assessment. To this end, it is critical to define the time between the occurrence of an actual event and the availability to the service provider and to the sponsor
- The list of AESI should remain adaptive along the study conduct depending on the potential detection of signal from any relevant source
- Appropriate linkages with in- and outpatients health records should be foreseen to ensure the highest level of case ascertainment
- If applicable, a system should be put in place to ensure timely individual case safety reporting to the relevant regulatory authorities (see Data reporting and submission section 3.5.)
- The proposal should ensure brand-specific vaccine exposure data capture. Depending on the countries, vaccine registries may be available, in which case, feasibility of linkage with subject individual data should be assessed. The feasibility of using other exposure data sources should also be assessed including the prospective collection of data available on vaccination cards, self-patient reporting with the use of self-reported pictures of the vaccination card, …
- The proposal should include a follow-up period of 3 months after vaccination with the first dose for medically-attended AEFI and 12 months for medically-attended AESI
- Approaches to avoid misclassification (such as: validity of case identification tools, medical ascertainment of the most important cases) should be explored and detailed in the proposal
- For each vaccine brand, the study start should be as soon as the SARS-CoV-2 vaccination start in the selected setting
- An estimation of the sample size according to requirements as described in the EMA Core RMP guidance (not available yet) and the frequency of AESI. All assumptions should be clearly described in the proposal.
- The service provider should also propose how optional analyses for providing estimates of risk measures for a specific AE (in a specific population), at the request of the sponsor (e.g. in case a signal or a question is raised by or to the MAH) could be performed
- The proposal should include a short summary of the statistical analysis plan (including its rationale) to detect and evaluate potential safety signals
- The proposal should explore the use of both primary and secondary data collection, separately or jointly, considering the above-listed criteria

3.4. Setting:

A multi-country model including several EU state members and UK is requested since it is expected that not all marketed vaccine brands will be available in one single country at the same time. The proposal should ensure representativeness in terms of brand-specific vaccine coverage.

3.5. Data reporting and submission:

Safety reporting to authorities: for primary data collection studies, regulations on reporting of adverse events as per GVP Module VI should be adhered to, which includes but is not limited to immediate reporting of serious adverse events to the concerned Vaccine Manufacturer/Marketing Authorization Holder.

Data sharing/reporting to the sponsors: a plan to conduct interim analyses and to generate interim statistical reports should be proposed in accordance to requirements as described in the EMA Core RMP guidance (not available yet). This plan should ultimately follow requirements as agreed between each MAH and EMA after submission and agreement on the risk management plan (RMP). In addition, a dashboard should be developed for real-time data sharing with the MAH and within the study team members, and for the purpose of monitoring progress of enrollment, data collection and validation.

Interim statistical reports should be populated (based on a cohort design):

- At month 1 after first enrolment or after enrolment of the first 1,000 subjects with at least 30 days post-first dose (if applicable), whichever comes first
- At month 3 after first enrolment or after enrolment of the first 5,000 subjects with at least 30 days post-first dose (if applicable), whichever comes first
- At month 6 after first enrolment or after enrolment of the first 10,000 subjects with at least 30 days post-first dose (if applicable), whichever comes first

Alternative interim reporting schedule may be proposed if other designs are used, i.e. based on the number of events (50, 100, …).

In case a signal is detected, an interim report should be populated and shared with the MAH within 7 days of date of signal detection.

4. Management

Please provide detailed descriptions and/or documentation to support the following in your proposal.

4.1. Project management

Describe the management and project team structure for the study and rationale for the proposed structure. Including:

- A description of key processes that you would use,
- Size and functions of the project team members as well as the reporting lines (please provide an organization chart)
- Short summary of roles and responsibilities of the project team members
- Summary of the governance: communication pathways and decision-making process, which include problem resolution and problem escalation, study risk management and mitigation plan
- CVs for key project members, including level of seniority
- Example of previous similar experiences

- If applicable a description of the process for the assessment and quality oversight of any subcontractors/third party vendors
- Please describe your approach to reporting and ensuring all relevant parties are timely apprised of relevant data and findings (see also section 3.5)

4.2. Study and Site Management

- Describe the subject recruitment and retention/data collection strategy/plan your team proposes for this study. Particular emphasis should be placed on the capacity to simultaneously enrolling subjects or collecting data in the different countries.
- If applicable, how (i.e. electronic, paper, web-based) data will be collected and verified? How would subject enrollment and screening be coordinated? Describe how brand and batch information will be collected and verified (in case of subject self-reporting, what exact tool will be used to capture and verify exposure, e.g. picture of vaccination card, linkage with vaccination registry,…?)
- In case of subject self-reporting activities, explain how case ascertainment will be conducted. Please explain how it will be compliant with General Data Protection Regulation (GDPR) and PV reporting requirements
- If applicable, please provide a communication and awareness plan for study promotion and subject recruitment.
- If applicable and referring to section 3.5., special attention needs to be put on the description of the management and process of expedited serious adverse events reporting
- If applicable, describe the site recruitment strategy your team proposes for this study, including identification, evaluation and selection. How will selection of study settings ensure that exposure to all vaccines of interest are captured? How would you manage non-enrolling sites? How adaptive will the site selection/activation be during the study conduct, which is highly dependent on national and supra-national vaccine distribution strategies (in other words, how will you ensure large scale site readiness?)
- Please describe your 'business continuity planning' during the pandemic, in particular solutions for maintaining contact with the patients/site coordinators if the usual process of data collection is not available or site visits are not possible.
- If applicable, describe the process of ethical document collection, review and approval.
- If applicable, describe the proposed methods/tools for study management and for site interactions, training, and management.
- If applicable, please describe the risk-based approach for site monitoring activities including site visits, data source verification process and frequency
- In the case secondary data collection data sources are used, please describe:
    - The process for data partner selection
    - The study data partner management and interaction process
    - The data extraction process (including data harmonisation, if applicable) and frequency
    - The quality control process
- Outline the timelines for study implementation considering vaccination may potentially start in Q1 2021.

4.3. Data management

- Describe how you propose to handle data capture, management, sharing and reporting.
    - Please include a list of those service providers with whom you intend to collaborate with for data management and your prior experience
    - Please include your preference for electronic data capture (EDC) and data management systems
    - Please describe the way you will ensure real-time data sharing with the MAH, through the development of a dashboard and other reporting tools
    - Please describe the data entry and verification process
    - Please describe the medical coding and data cleaning process, including medical review plan
- Describe the current study database readiness considering a study start in Q1 2021
- If applicable, describe the current digital tool readiness for data capture

4.4. Data protection and privacy

Describe how you would address patient protection and data confidentiality at the patient and manufacturer levels. Please include:

- Methods for obtaining informed consent
- Patient-level data protection measures
- The aggregate and individual patient-level data that will be shared with each manufacturer and how
- Manufacturer-level data protection measures
- How data will be delivered to each manufacturer

4.5. Quality control and standard operating procedures

Please describe your proposed means of quality control and standard operation procedures for the proposed approach at all study levels and stages.

4.6. Regulatory and ethical compliance

The CRO/Service provider should follow GPP/GVP/ENCePP guidelines applicable to the non-interventional epidemiological studies, which, for primary data collection studies, includes but not limited to immediate reporting of serious adverse events to the concerned Vaccine Manufacturer/Marketing Authorization Holder. In the report adverse events defined as potential risks in the Risk Management Plans of the vaccines of interest and all other unsolicited reactions should be specified. Processes of obtaining ethical approval should be described and specify how this will be dealt with in the context of a multiple sites across multiple regions, if applicable as well as the timeframes of ethical approval.

5. Study feasibility assessment

Based on the criteria listed in section 3 and 4, please describe the results of your preliminary study feasibility assessment including both technical and operational aspects. Particular emphasis should be placed on:

- the capacity to initiate the study by Q1 2021

- the capacity (resources, logistic…) to operationalize multiple studies (both simultaneously and sequentially)
- the testing of the tools and study procedures that have been developed so far to:
    - appropriately capture and ascertain brand-specific vaccine exposure and safety events of interests
    - reach the necessary sample size including representativeness of both general and special populations (health care workers, pregnant women, risk groups, …)

6. Timelines

This RFP is dated 18th November 2020. The proposers should send their proposal to 5.1.2e 5.1.2e (5.1.2e @efpia.eu), 5.1.2e and 5.1.2e 5.1.2e (5.1.2e @gsk.com) 5.1.2e

In case the Service Provider has any question regarding this RFP, they should be submitted anonymized in one consolidated document to 5.1.2e 5.1.2e and 5.1.2e 5.1.2e and received no later than close of business on November 24th, 2020. Vaccines Europe will respond to all questions by close of business on November 27th, 2020.

Proposals are due no later than December 3rd, 2020.

Proposers should detail their budget in an excel sheet (Appendix 1) using items as specified in Table 1 (Budget specification; section 7). Currency for the budget proposal should be in EUROS. Table 2 (Scope of work), which can be found in section 8 'Tables', should also be completed as a part of the proposal. Items as detailed and proposed in Appendix 1 and Tables 1 and 2 may be adapted according to the proposed study design and data sources.

Proposals will be evaluated immediately thereafter by Vaccines Europe and, individually by all Vaccine Manufacturers participating to the COVID-19 vaccine working group of Vaccines Europe. Potential contracts resulting from successful proposals will be made between the Service Provider and interested Vaccine Manufacturers on an individual basis.

7. Budget

Please fill up Table 1 and Appendix 1 to specify the requested budget to conduct the study. Please note that Table 1 mainly follows the structure of a primary data collection data source type of study. In case secondary data collection is used as the primary data source or to complement primary data collection, please adapt the different items accordingly.

Table 1 Budget specifications (please add additional rows if more than 1 person is involved in the task)

Task	Resource involved and position per	Hourly rates	Total hours needed per task, fixed and per subject	Unit cost/Number of unit and total costs	Costs, fixed and per subject, where applicable

	region		where applicable		
Project Set Up Activities (where applicable specify preparation, review approval etc)	1. 2. 3. etc	1. 2. 3. …. etc			
Core Protocol development (2 drafts + final version) (English version)					
SAP development (2 drafts + final version)					
MAH specific protocol development (1draft + final)					
MAH specific SAP development (1draft + final)					
Feasibility assessment (technical and operational)					
Regulatory submissions (specify Health Authorities, ethical committees, etc) including Initial file preparation, review and submission					
Posting on Public Registry (ENCEPP, Clinicaltrials.gov, and other regional/national registries, if applicable)					
Case Report Form (CRF) and related documents (English version)					
If applicable, Informed consent form (English version)					
If applicable, any other study document					
If applicable, study documents					

Translation					
Project Management & Team Meetings					
Meeting organization (internal, external)					
General Project Management and Monitoring					
Communication Plan (e.g. frequency of regular communication, status report…)					
Study risk management plan					
Set-up and Maintenance of Study Master File, including Archiving of study documents at the end of the study					
Awareness and promotion Materials					
Communication plan					
Awareness and promotion Materials					
Study monitoring					
Monitoring guidelines/data partner oversight guidelines					
Site/data partner initiation					
Monitoring/data partner oversight visit (remote)					
Protocol deviation and escalation management plan					
Close out visit					
Data Management/Programming Ongoing Activities					
Digital solution development and					

testing					
Database Design/Review/Build/Testing					
Data Validation and related process and management documents					
Data security					
Data management plan					
Database Maintenance					
Data Entry and Verification					
Data Cleaning					
Medical Coding					
Adverse events reconciliation					
Data Imports from External Vendors, if applicable					
Database lock and data reports					
Data Transfers					
Database quality control					
Archival					
Adverse Event Management					
If applicable, adverse event report form development					
If applicable, immediate Reporting of serious adverse events to vaccine manufacturer/Marketing Authorization Holder					
Study sites/data partners selection and management					
Investigator/Site/data partner selection					

Investigators / data partner contract management					
Investigators payment/ data partner (if applicable)					
Biostatistics					
Study size assessment					
Programming of Analysis Files and Table/Listing/Figure Shells					
Periodic and final statistical analyses					
Optional analyses for providing estimates of risk measures					
Reporting					
Interim report					
Final Report (ghost report + 2 drafts + final version)					
Quality Assurance and Audits					
Maintain 'audit trail' of recruitment, enrollment, follow-up and reporting processes (i.e., contacts, dates, information obtained, etc.).					
Quality assurance procedures (including existing SOPs)					
Audit and inspection management					

8. Tables

Please complete below Table 2 on the Scope of Work as part of the proposal to this RFP. Please adapt the items of Table 2 to align items with Table 1 as appropriate.

Table 2 Scope of work

Task	Vaccine manufacturer	CRO	Sub-contractor of CRO
Project Set Up Activities (where applicable specify preparation, review approval etc)	1. 2. 3. etc	1. 2. 3. …. etc	
Core Protocol development (2 drafts + final version) (English version)			
SAP development (2 drafts + final version)			
MAH specific protocol development (1draft + final)			
MAH specific SAP development (1draft + final)			
Feasibility assessment (technical and operational)			
Regulatory submissions (specify Health Authorities, ethical committees, etc) including Initial file preparation, review and submission			
Posting on Public Registry (ENCEPP, Clinicaltrials.gov, and other regional/national registries, if applicable)			
Case Report Form (CRF) and related documents (English version)			
If applicable, Informed consent form (English version)			
If applicable, any other study document			
If applicable, study documents Translation			
Project Management & Team Meetings			
Meeting organization (internal, external)			

General Project Management and Monitoring			
Communication Plan (e.g. frequency of regular communication, status report…)			
Study risk management plan			
Set-up and Maintenance of Study Master File, including Archiving of study documents at the end of the study			
Awareness and promotion Materials			
Communication plan			
Awareness and promotion Materials			
Study monitoring			
Monitoring guidelines/data partner oversight guidelines			
Site/data partner initiation			
Monitoring/data partner oversight visit (remote)			
Protocol deviation and escalation management plan			
Close out visit			
Data Management/Programming Ongoing Activities			
Digital solution development and testing			
Database Design/Review/Build/Testing			
Data Validation and related process and management documents			
Data security			
Data management plan			
Database Maintenance			
Data Entry and Verification			

Data Cleaning			
Medical Coding			
Adverse events reconciliation			
Data Imports from External Vendors, if applicable			
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Database quality control			
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Adverse Event Management			
If applicable, adverse event report form development			
If applicable, immediate Reporting of serious adverse events to vaccine manufacturer/Marketing Authorization Holder			
Study sites/data partners selection and management			
Investigator/Site/data partner selection			
Investigators / data partner contract management			
Investigators payment/ data partner (if applicable)			
Biostatistics			
Study size assessment			
Programming of Analysis Files and Table/Listing/Figure Shells			
Periodic and final statistical analyses			
Optional analyses for providing estimates of risk measures			
Reporting			

Interim report			
Final Report (ghost report + 2 drafts + final version)			
Quality Assurance and Audits			
Maintain 'audit trail' of recruitment, enrollment, follow-up and reporting processes (i.e., contacts, dates, information obtained, etc.).			
Quality assurance procedures (including existing SOPs)			
Audit and inspection management			

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MAH specific SAP development (1draft + final)			
Feasibility assessment (technical and operational)			
Regulatory submissions (specify Health Authorities, ethical committees, etc)			

Posting on Public Registry (ENCEPP, Clinicaltrials.gov, and other regional/national registries, if applicable)			
Case Report Form (CRF) and related documents (English version)			
If applicable, Informed consent form (English version)			
If applicable, Local ICF and study documents Translation			
Project Management & Team Meetings			
Meeting organization (internal, external)			
General Project Management and Monitoring			
Communication Plan (e.g. frequency of regular communication, status report…)			
Compliance management			
Set-up and Maintenance of Study Master File, including Archiving of study documents at the end of the study			
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Maintain 'audit trail' of recruitment, enrollment, follow-up and reporting processes (i.e., contacts, dates, information obtained, etc.).			
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Audit and inspection management			

8. Appendix I

Budget specification excel spreadsheet.