DRIVE
Development of Robust and Innovative Vaccine Effectiveness

4.2.19

Call for tenders – 2019/20 influenza season

Measuring brand-specific influenza vaccine effectiveness in EU/EEA

Tender Specifications

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About DRIVE

The IMI JU project DRIVE (www.drive-eu.org) aims to create a European platform for studying brand-specific influenza vaccine effectiveness (IVE) and to develop a governance model for scientifically robust, independent and transparent studies in a public-private partnership. The entities participating in DRIVE are public health institutes, universities, research organisations, small and medium-sized enterprises and members of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

In DRIVE, data from several independently operating national or regional study sites are analysed jointly to obtain a large geographical coverage and sufficient sample size for brand-specific IVE estimation.

Decision-making in DRIVE is shared between public and private partners; however, the IVE studies themselves are led by public institutions independently of vaccine manufacturers. An Independent Scientific Committee oversees the process.

For the 2018/19 season, a total of 13 sites have joined the DRIVE platform and contribute data using both test-negative and cohort study designs. The results of DRIVE's pilot study in the 2017/18 season are available on the DRIVE website.

In 2019, the DRIVE network will continue to evolve. Any organization, institution and network meeting the eligibility criteria may apply to join the consortium as a Research Collaborator through this call for tenders. For public sector organizations who already conduct IVE studies there are also other options to contribute to the project; please see the DRIVE website for more information.

Background

Influenza is a major public health burden. It is responsible for 50 million disease episodes and 15,000 to 70,000 deaths in the European Union (EU) and European Economic Area (EEA) Member States each year, although with considerable variation from season to season [2] and by outcomes used [3]. Complications including deaths are more common in the elderly and in children younger than one year of age [4]. Vaccination is considered the most effective means for preventing influenza and its complications and the World Health Organization (WHO) has set a vaccination coverage target of at least 75% in the elderly population and among risk groups. [5]

Due to frequent genetic and antigenic changes in influenza viruses, the seasonal vaccine is reformulated each year and annual revaccination is recommended. Observed IVE varies from year to year due to a variety of reasons including mismatch between the vaccine virus strains and the circulating strains, waning immunity and possible interference from previous

vaccinations [6, 7]. In the last two decades, controversies have sprung around the effectiveness of influenza vaccines [8]. While past IVE estimation efforts have led to significant achievements using generic protocols, standard methodologies and laboratory confirmation, several questions about IVE remain open.

In its new guideline on influenza vaccines, the European Medicines Agency (EMA) [9] requires that observational IVE studies be conducted in the EU/EEA as part of the post-licensure commitments of the vaccine manufacturers. EMA expects the studies to be conducted in line with Good Epidemiological Practice (GEP) guidelines and with European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP) guidelines; to reach this goal, manufacturers are encouraged to liaise with organisations / institutions / public health authorities.

About the tender

The purpose of this tender is to evolve the DRIVE network by including new study sites capable of estimating IVE.

DRIVE is proposing to the applicants a status of Research Collaborator for one-year duration (from 1 July 2019 to 31 June 2020), thereafter eligible for renewal annually based on the needs of the project and the willingness of the research collaborator.

DRIVE will ask the Research Collaborators to share relevant data with DRIVE (based on the proposal) and to contribute to their integration into the pooled analysis.

The data collected for DRIVE specific needs/objectives should be provided to P95, the DRIVE partner responsible for the pooled analysis, located in Belgium. The Research Collaborator will remain the owner of the data. Data generated by the Research Collaborator will be accessible only to the non-EFPIA partners of DRIVE for scientific review and pooled analysis purposes (i.e. no access by the industry) and, if necessary, to a third party (independent auditor) commissioned by DRIVE's Quality Control and Audit Committee for auditing purposes.

The Research Collaborator will be compensated by FISABIO (the DRIVE Coordinator) for the data sharing and contribution to the analysis and for its participation in project meetings as agreed beforehand. The allocated budget will be appropriately sized to the related work; double funding (the situation where the same activity would be funded twice from different sources) will not be possible.

The benefits to the Research Collaborator include:

- Generating robust brand-specific IVE in a European network
- Implementing potentially innovative approaches for IVE studies

- Participation in the scientific discussion and publication process
- Receiving capacity building and funding (as applicable)
- Participation in the DRIVE Annual Forum and General Assembly.

The terms and conditions of the collaboration will be formalized through a Research Agreement between the Research Collaborator and FISABIO (DRIVE Coordinator).

Eligibility criteria

Any organisation, institution or network with interest and expertise/capacity to perform influenza vaccine effectiveness studies in Europe is eligible to participate in the DRIVE call for tenders.

To fulfil the admissibility requirements the applicants should

- Fill in the provided template with basic information of the applicant and their previous work in the field of influenza and/or vaccines
- Provide a technical and financial proposal to describe the work that is to be done. Other relevant documents which may support their proposal (study protocol, data specifications…) may be annexed.

Upon receiving the application, DRIVE may ask for clarifications or changes to the proposal or ask the applicant to provide additional documents. Completing the procedure of the call for tenders does not impose on DRIVE any obligation to award a contract.

Tender timelines

The call opens in February. Proposals should be submitted at the latest on **April 15th 2019** to DRIVE (by email to info@drive-eu.org). Any questions about DRIVE will be answered at info@drive-eu.org while the application period is open.

Official responses from DRIVE indicating whether or not the proposals are selected will be sent to applicants at the latest on **June 17th 2019** with the proposed allocated funds from DRIVE to the selected proposals.

FISABIO will contact the selected sites to discuss legal and operational details of the collaboration in July 2019, and will organise a site visit/meeting when appropriate. The selected sites will be invited to participate to the Consortium's Annual meeting in **July 17–18 2019** in Helsinki, Finland).

Evaluation and selection

Proposals will be reviewed in a stepwise approach:

1. The Independent Scientific Committee of DRIVE (see description on DRIVE website) will perform the scientific evaluation of the proposals based on predefined criteria (please see below).

2. The Steering Committee of DRIVE will make the strategic selection of the proposals and will decide the budget allocation. This committee is composed of members of the DRIVE partner who have equal voting rights with a 50/50 parity between public consortium and EFPIA partners.

The scientific evaluation of the Research Collaborator's proposal will be made by the Independent Scientific Committee uses the following scoring criteria:

- Ability to adhere to DRIVE generic protocols or level of appropriateness for DRIVE for innovative studies (15 points)
- Ability to capture brand-specific information (10 points)
- Estimated sample size; overall and exposed subjects (10 points)
- Scientific reliability of the laboratory testing or ability to send samples for DRIVE testing (10 points)
- Expertise in epidemiology and/or IVE studies (5 points)

The Steering Committee will evaluate the proposals' relevance by each of the following aspects:

- ISC scientific evaluation and recommendations
- Ability to fill gaps in DRIVE's existing data collection (e.g. brand coverage, age group respresentation) and relevance for pooled analysis in DRIVE
- Whether collaborator represents a new partner institution / country
- Cost-effectiveness / Co-funding / sustainability

Relative to the efforts needed to contribute to the DRIVE studies, the indicative funding range per proposal is 10 000–50 000 EUR for secondary use of already collected data (depending on sample size) and 50 000–150 000 EUR for new primary data collection, capacity building and innovative approaches (depending on study design and sample size). The allocated budget will depend on the proposal and be appropriately sized to the related work. The maximum budget available for all tendered studies in the 2019/20 season is 1 000 000 EUR. DRIVE reserves the right to not award the whole budget.

Upon receiving the financial proposal, DRIVE may request clarifications or changes. DRIVE has no obligation to award the full amount requested by the applicant. Even if DRIVE may cover the full cost of the applicant activities for some proposals, the level of possible co-funding is a criterion for the selection.

Technical specifications

Scope

The scope of this tender is to assess influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza (LCI), by vaccine brand. Ideally, the assessment should also be specific to influenza strain/subtype/lineage/clade, age group, vaccination target- and risk group; and provide estimations according to time window in the epidemic season (early, middle, end), time

since vaccination, and by previous influenza vaccinations. Other, non-specific endpoints such as ILI, SARI and pneumonia may be considered in addition to LCI.

The applicant should propose to conduct the study according to one of the DRIVE generic study protocols (ANNEX 1&2) adapted to the local specifications unless the study is considered innovative (see Innovation).

The applicant should provide DRIVE consortium with a dataset containing anonymized/pseudonymized or aggregated information on exposure (vaccination), outcome (influenza) and other variables of interest (see ANNEXES 1&2, minimum dataset requirements/codebook sections). The ownership of the data will remain with the applicant. The contributed data will be processed without the involvement of vaccine manufacturing authorization holders, and will under no circumstances be transferred to vaccine manufacturers. The applicant will be free to publish their own results separately from the DRIVE pooled analysis. DRIVE funding for primary data collection should be acknowledged as per ICMJE guidelines and DRIVE should receive the publication for non-binding comments.

Brand-specificity
Availability of vaccine brand information is critical for DRIVE. Brand should preferably be directly indicated in the data. Where this is not possible, IVE should be provided by vaccine type: by vaccine antigen (live attenuated, split virion, subunit), by valency (number of vaccine virus strains) or adjuvant (adjuvanted vs. non-adjuvanted) or where not possible, overall IVE. When vaccine brand information is not supplied as part of the dataset, the applicant should specify how the information can be inferred otherwise (e.g. if only a single vaccine brand is used in the area).

The applicant should, if this information is available and can be shared publicly, include the information on which vaccine brand(s) are expected to be used in the area for influenza season 2019/20 or specify the local bodies holding this information.

Answering data gaps
DRIVE aims to cover as many influenza vaccine brands as possible, in different target groups of vaccination. Therefore, one of the selection criteria is related to the ability of the contractor to provide data that is currently not adequately provided by DRIVE studies.

The applicant should provide their estimation of the expected number of LCI/ILI for the season of interest per vaccine type/brand by age group (children/adult/elderly) and setting (primary care / hospital). It could be based on the figures from the previous season adjusted by an estimated distribution by vaccine types/brands for the season of interest.

Innovative/alternative methodologies

DRIVE seeks to develop novel and innovative methods to assess IVE. Examples include (but are not limited) to participatory epidemiology, use of novel data sources, novel endpoints, novel statistical methods, and combining conventional and novel methods in hybrid systems.

In order to be considered, an innovative approach should increase the quality and/or have cost-saving potential over existing IVE study approaches. Some examples are listed in the table below. Please also refer to DRIVE D7.3: Report on feasible, novel and innovative approaches for measuring influenza VE, available on the DRIVE website (pdf).

Table: possible methods considered by DRIVE

Open data: Making better use of existing data to determine IVE
IVE using rapid near-patient molecular tests
Improved IVE estimation in hospitals, e.g. through systematic swabbing
Non-specific influenza outcomes to estimate IVE
High-dimensional propensity scores to control for confounding in large register-based studies
Ontological approach for identifying influenza cases across heterogenous data sources
Participatory surveillance / self-swabbing to determine IVE
Using negative control outcomes to detect residual confounding

Reference documents

IVE studies utilizing the test-negative design and population-based databases will need to adhere to DRIVE generic research protocols (ANNEX 1 & 2, respectively). The datasets provided will aim at maximum possible adherence to the DRIVE minimum dataset requirements (codebook) supplied as part of the protocols.

A study protocol (based on a DRIVE generic protocol) should be submitted to DRIVE at the latest by 30 September 2019. Dataset (individual level or aggregated data) should be submitted to DRIVE at the latest by 15 May 2020; when applicable, a preliminary dataset for interim analysis should be submitted to DRIVE by 31 January 2020. The local study report should be submitted by 30 June 2020.

Study design & setting

The study designs used may include

- Case-control study using the test-negative design
- Cohort study using electronic databases
- Other study designs, including prospective cohort studies and novel and innovative designs.

The settings used to study IVE may include

- General practitioner setting (GP), or a network of GPs
- Hospital setting
- Population-based databases
- Other study settings.

The applicant should describe in the proposal in detail the study setting and population including age distribution, influenza vaccine coverage, and laboratory methods used to detect influenza. For all studies conducted, laboratory-confirmation of influenza by an accredited laboratory shall be ensured and documented, except when agreed otherwise with the DRIVE Coordinator.

The lab involved in the studies should:

- Be able to detect influenza by RT-PCR (however, DRIVE may investigate the value of other methods of influenza virus detection in innovative study designs). Further characterization of the detected virus by sub-typing (for Influenza A viruses) and lineage determination (Influenza B viruses) is strongly recommended.
- Have their performance assessed by participation in External Quality Assessment (EQA) such as those provided by Quality Control for Molecular Diagnostics (QCMD) and be able to provide (if possible) a certificate for accreditation. If such accreditation cannot be provided, the applicant can engage with DRIVE to discuss potential alternatives.

Optionally, the lab involved could further add value to the study by carrying out additional influenza testing:

- Genotyping of the virus (HA and NA gene sequencing, by Sanger or NGS, for genetic clade determination; full genome sequencing can also be an objective)
- Strain characterization for the identification of potential antigenic variants. This means being able to grow influenza viruses on MDCK cells, and subsequently determine their antigenic profile with ferret sera.

OR

- Arranging for samples to be transferred to a DRIVE partner's laboratory for such analysis.

Ethics

The applicant shall ensure and collect any necessary ethical committee approvals for all study sites. The applicant should be compliant with their ethical and local regulations for the conduction of study or for the secondary use of their data; any obligation related to data protection and data transfer to the DRIVE network (P95, Belgium) should be anticipated. The data will be stored on a secure server (as per the DRIVE Data Management Plan).

All research activities should be organised in accordance with relevant national and EU legislation (including General Data Protection Regulation), the Declaration of Helsinki, the Convention of Council of Europe on Human Rights and Biomedicine, the Ethical Rules of the Seventh Framework Programme, and, where applicable, the ADVANCE Code of Conduct, ENCePP Code of Conduct, Opinions of European Group on Ethics in science and new technologies, Good Epidemiological Practice, Guidelines for Good Pharmacology Practices and the standards of the International Conference on Harmonisation on Good Clinical Practice.

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Annexes

1. Proposal template
2. DRIVE D7.1 Core protocol for type/brand-specific influenza vaccine effectiveness studies (test-negative design studies)
3. DRIVE D7.2 Core protocol for type/brand-specific influenza vaccine effectiveness studies (population-based database cohort studies)

The annexes are available at http://www.drive-eu.org/.