DRIVE
Development of Robust and Innovative Vaccine Effectiveness

25.5.18

Call for tenders – 2018/2019 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 will be jointly analysed 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 without involvement of vaccine manufacturers and an Independent Scientific Committee oversees the process.

During the influenza season 2017/18, the DRIVE partners in Italy, Finland and Spain have been collecting IVE data in both test-negative case-control studies and population-based cohort studies.

Starting from influenza season 2018/19, the DRIVE network will be expanded in two ways. National or regional public health institutes may join DRIVE as Associate Partners (more information about this process available at www.drive-eu.org). Additionally, any organization, institution and network meeting the eligibility criteria may join through this call for tender.

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 methodology used [3]. Complications including deaths are more common in the elderly and in children younger than one year of age [4]. Vaccination is considered as the most effective means for preventing influenza and its complications [5] and the World Health Organization (WHO) has set a vaccination coverage target of at least 75% in the elderly population and among risk groups [6].

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 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 extend the DRIVE network by including new study sites capable of producing IVE estimates. Tenders are awarded in two categories: *Starting a new study* & *Contributing with an existing study.*

DRIVE is proposing to the applicants a status of Research Collaborator for one year duration (from 1 August 2018 to 31 July 2019) renewed annually based on the needs of the project and the willingness of the partner.

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/meta-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/meta-analysis purposes (i.e. no access by the industry) and, if necessary, to a third party contract research organization (CRO) 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 through a network
- Implementing potentially innovative approaches for IVE estimation
- Participation in the scientific discussion and publications process
- Receiving funding for their data collection (as applicable) and capacity building
- 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 on 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

Proposals should be submitted at the latest on **June 25th 2018** 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 will be sent to applicants at the latest on **July 6th 2018** 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 beginning of July 2017, and will organise a site visit/meeting when appropriate. The selected sites will be invited to participate to the Consortium Annual meeting in September 17-18th 2018 in Rome).

Evaluation and selection

Proposals will be reviewed by the Steering Committee of DRIVE. This committee is composed of members of the DRIVE partner's leads who have equal voting rights with a 50/50 parity between public consortium and EFPIA partners.

The evaluation and selection of the Research Collaborators will be made by the Steering Committee using the following scoring criteria:

NEW STUDIES	Points
Relevant expertise and experience of the applicant • Expertise in the conduction of epidemiological studies (5 pts) • Experience in the conduction of influenza vaccine effectiveness studies (5 pts)	10
Proposed research collaboration for DRIVE • Scientific relevance and quality of the system, including ability to adhere to DRIVE protocols and collect brand-specific information (10 pts) • Sample size, targeted population/group and geographical representation and ability to answer DRIVE gaps (20 pts)	30
Cost-effectiveness and level of possible co-funding from the applicant	10
Supplementary points (Bonus) for innovative approach	(+20)
Total maximum	50

EXISTING STUDIES	Points
Proposed research collaboration for DRIVE	30

• Scientific relevance and quality of the system, including ability to adhere to DRIVE protocols and collect brand-specific information (10 pts) • Sample size, targeted population/group and geographical representation and ability to answer DRIVE gaps (20 pts)	
Cost-effectiveness and level of possible co-funding from the applicant	10
Total maximum	40

The indicative funding range per proposal is 10 000–50 000 EUR for secondary use of data (depending on sample size) and 50 000–150 000 EUR for new 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 total budget available for all tendered studies in the 2018/19 season is 1 000 000 EUR. DRIVE reserves the right to not to 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 applying as an innovative study (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). The ownership of the data will remain with the applicant. The contributed data will be processed within DRIVE Work Package 7 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. DRIVE funding for primary data collection should be acknowledged as per IJCME guidelines and DRIVE may receive the publication for non-binding comments.

Categories

The applicant may submit the tender in one of two categories:

- **1. Starting a new study.** This category is for sites that have not assessed IVE before, or want to set up a novel way of doing so. DRIVE may provide resources to set up an IVE study e.g. on an existing influenza surveillance platform. The study may follow a conventional design (e.g. TND or cohort, using DRIVE protocols) or include novel elements.
- **2. Contributing with an existing study.** This category is for sites with existing IVE study capacity (e.g. using TND or cohort design).
    - a. with modifications to data collection required for DRIVE.
    - b. without modifications to data collection

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 if 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 2018/19 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.

Innovation

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.

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 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 2018. Dataset or the aggregated data should be submitted to DRIVE at the latest by 30 April 2019; when applicable, a preliminary dataset for interim analysis should be submitted to DRIVE by January 31 2019. The study report should be submitted by 30 June 2019.

Study design & setting

The study designs used may include

- Case-control setting using the test-negative design
- Cohort study using electronic databases
- Other study designs, including novel and innovative designs, in agreement with DRIVE Coordinator.

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, in agreement with DRIVE Coordinator.

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 (first line of screening), even if DRIVE will investigate the value of other methods of influenza virus detection in innovative study designs.
- Further characterize the detected virus by sub-typing (for Influenza A viruses) and lineage determination (Influenza B viruses).
- Have their performance assessed by participation in External Quality Assessment (EQA), as those provided by Quality Control for Molecular Diagnostics (QCMD).
- If possible, the lab may also carry out additional influenza testing such as genotyping of the virus or strain characterization for the identification of potential antigenic variants.

Sites not currently meeting some of these requirements may still apply in category 1. *Starting a new study.*

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. 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.

References

1. World Health Organization. A manual for estimating disease burden associated with seasonal influenza. Geneva, Switzerland, http://apps.who.int/iris/bitstream/10665/178801/1/9789241549301_eng.pdf (2015).
2. Uhart M, Bricout H, Clay E, et al. Public health and economic impact of seasonal influenza vaccination with quadrivalent influenza vaccines compared to trivalent influenza vaccines in Europe. Hum Vaccin Immunother; 12: 2259–2268, https://www.tandfonline.com/doi/full/10.1080/21645515.2016.1180490 (2016).
3. Nicoll A1, Ciancio BC, Lopez Chavarrias V, Mølbak K, Pebody R, Pedzinski B, Penttinen P, van der Sande M, Snacken R, Van Kerkhove MD. Influenza-related deaths--available methods for estimating numbers and detecting patterns for seasonal and pandemic influenza in Europe. Euro Surveill. 2012 May 3;17(18). pii: 20162.
4. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations Associated With Influenza and Respiratory Syncytial Virus in the United States, 1993–2008. Clin Infect Dis; 54: 1427–1436, https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/cis211 (2012).
5. World Health Organization. Fact sheet Influenza (Seasonal), http://www.who.int/mediacentre/factsheets/fs211/en/ (2016).
6. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis; 12: 36–44, http://www.ncbi.nlm.nih.gov/pubmed/22032844 (2012).
7. Ramsay LC, Buchan SA, Stirling RG, Cowling BJ, Feng S, Kwong JC, Warshawsky BF. The impact of repeated vaccination on influenza vaccine effectiveness: a systematic review and meta-analysis. BMC Med. 2017 Aug 21;15(1):159. doi: 10.1186/s12916-017-0919-0.
8. McCartney M. What use is mass flu vaccination? BMJ; 349: g6182, http://www.ncbi.nlm.nih.gov/pubmed/25331457 (2014).
9. Committee for Medicinal Products for Human Use. Guideline on Influenza Vaccines – Non-clinical and Clinical Module. Eur Med Agency EMA/CHMP/VWP/457259/2014; 44: 1–31, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167817.pdf (2016).

Annexes

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

The annexes will be available at http://www.drive-eu.org/index.php/results/deliverables/.