DRIVE
Development of Robust and Innovative Vaccine Effectiveness

01.03.2021

Call for tenders – 2021/22 influenza season

Measuring brand-specific influenza vaccine effectiveness in EU/EEA

Tender Specifications

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About DRIVE

The Innovative Medicines Initiative 2 Joint Undertaking (IMI JU) project DRIVE (Development of Robust and Innovative Vaccine Effectiveness, 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 vaccine companies.

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 (issues related to project execution, technical development, work plan updates, and effort/budget reassignment in order to pursue optimal efficiency) is shared between public and private partners, which are equitably represented in the DRIVE Steering Committee; however, the IVE studies themselves are led by public institutions and vaccine companies have no role in the data collection, analysis and preparation of the report including interpretation of the results. Vaccine companies partners are provided the option to review and provide written comments to the scientific deliverables (protocol, statistical analysis plan, report). An Independent Scientific Committee (ISC) oversees the process to guarantee the scientific robustness of the studies and avoid perception of undue influence by vaccine companies of IVE results.

DRIVE research collaborators contribute by providing data using both test-negative and cohort study designs. The results of DRIVE's previous seasons (2017/18, 2018/19, 2019/20) are available on the DRIVE website.

An increasing number of sites are joining DRIVE study platform every year: the network initially expanded from 4 sites on the pilot season (2017/18) to 13 sites on 2018/19 season and a total of 15 sites joined the DRIVE platform for 2019/2020 season. Despite the COVID-19 pandemic arising in Europe in late February 2020, the previous study tender was launched allowing the expansion of the DRIVE network for the season 2020/21 with 7 new hospitals (expansion of the IREIVAC and Vall d'Hebron hospital networks) and 3 new study sites (Iceland Directorate of Health joined as Associated Partners and 2 new study sites in Spain).

While we recognize the impact of COVID-19 on the current influenza circulation and the projection for the upcoming season remains uncertain, understanding influenza vaccine effectiveness remains important, especially if co-circulation would occur. Hence for the season 2021/22 the DRIVE network aims to continue evolving. Any organization, institution and network meeting the eligibility criteria are encouraged to apply to join the consortium as a Research Collaborator through this call for tenders. For Public Health Institutes and research institutes who already conduct IVE studies there is the possibility to contribute to the project as associate partners (they can join at any moment of

the season and share data they are collecting from the existing surveillance system in place in their country/area); 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 vaccines are regularly reformulated (almost every year) based on the WHO recommendations and annual vaccination 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, several controversies have sprung around the performance of influenza vaccines in real word settings (referred later on as Influenza Vaccine Effectiveness or IVE) [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 guideline on influenza vaccines that into effect in February 2017, the European Medicines Agency (EMA) [9] requires that post-authorisation effectiveness studies should be included in the Risk Management Plan as additional pharmacovigilance activities for all influenza seasonal and pandemic vaccines including currently authorized and new influenza vaccines. IVE studies are preferably to be conducted in the EU/EEA as part of the post-licensure commitments of the vaccine companies. EMA expects the studies to be conducted in line with GxPs including good pharmacovigilance practices (GVP) with Good Epidemiological Practice (GEP) guidelines and with European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP) guidelines; to reach this goal, vaccine companies are encouraged to liaise with organisations / institutions / public health authorities who have experience in influenza effectiveness studies and who have implemented a functioning infrastructure to conduct multicentre studies.

About the tender

The purpose of this tender is to expand the DRIVE network by on-boarding new Research Collaborators capable of estimating brand-specific IVE.

DRIVE is proposing to the applicants a status of Research Collaborator for one-year duration (from 1 July 2021 to 31 June 2022), thereafter eligible for

renewal annually based on the needs of the project and the willingness of the research collaborator to pursue the collaboration.
DRIVE will ask the Research Collaborators to share relevant data with DRIVE (based on the proposal) and to contribute to their integration into the annual pooled analysis.
The data collected for DRIVE specific needs/objectives should be provided to P95 (a DRIVE partner accountable for the data transfer and analysis), via a secured electronic study support application (ESSA), 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 analytical team (P95) for data quality control and pooled analysis purposes (i.e. no access by the vaccine companies) and, only if deemed 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 for the data sharing and contribution to the analysis and for its participation in project meetings as agreed beforehand. The funds for this compensation come from the allocated IMI budget secured for the DRIVE project. FISABIO (the DRIVE public Coordinator) manages contracts and legal aspects. The allocated budget will be appropriately sized to the related work and the contribution to the sample size for the pooled analysis according to pre-existing benchmarks; 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:

- Contribute to the generation of robust brand-specific IVE in a European network.
- Implementing potentially innovative approaches for IVE studies.
- Participation in the scientific discussions 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).

Important note: DRIVE Call for tenders updated

Advised by the European Medicines Agency (EMA) and the Innovative Medicines Initiative (IMI), DRIVE will adapt its European brand specific IVE platform to address the COVID-19 situation. Therefore, the annual study tender has been updated to encompass data collection on SARS-CoV-2 infection which will be essential to interpret its impact on the IVE assessment. EMA and IMI representatives also agreed on the recommendation for a more targeted and pragmatic approach prioritizing adult and older adult populations and hospital settings in order to obtain more reliable IVE data. Accordingly, the

annual DRIVE call for tenders was updated in 2020 and **only studies focused on adult/older adult populations in hospital settings will be included in the selection process**. Although the Call for tenders has switched focus on hospital/adults, DRIVE will continue to perform IVE analysis on Primary care setting and children leveraging the data of DRIVE Consortium public members and Associated Partners.

DRIVE has adapted its protocols, SAP and operational aspects to the influence of COVID-19 in the influenza circulation, as COVID-19 is substantially impacting the IVE studies. Therefore, it is requested to the sites **to share COVID-19 related data** as a valuable new condition.

Eligibility criteria

Any organisation, institution or network with interest and expertise/capacity to perform brand-specific influenza vaccine effectiveness studies targeting adult/older adult populations in the hospital setting within Europe is eligible to participate in the DRIVE call for tenders. To fulfill 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.

Exclusion criteria

All proposals that meet the following will be excluded from the evaluation process:

- Studies focusing exclusively or largely on primary care settings or General Practitioner networks;
- Studies focusing exclusively or largely on children or on special populations (for example healthcare workers or pregnant women);
- No brand-specific information captured or possible to be retrieved;
- IVE studies focusing exclusively on vaccines registered under national procedures only (in a single country);
- Impossibility to confirm the influenza cases by laboratory test

Tender timelines

The call is **launched on the first week of March 2021**. Proposals should be submitted at the latest on **May 14th 2021** 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. During the evaluation and selection

process queries will be sent to sites to collect additional information or obtain further clarifications.
Formal decision from DRIVE indicating whether the proposals are selected will be communicated to applicants at the latest **during July 2021** 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 2021 and will organise a site visit remotely (via virtual meeting) when appropriate/possible.

Evaluation and selection

Proposals will be reviewed according to the following stepwise approach:

1. The Independent Scientific Committee of DRIVE (ISC) (see description on DRIVE website) will perform the scientific evaluation of the applicant proposals based on predefined criteria (as detailed below).
2. The Steering Committee (SC) of DRIVE will make the strategic review of the proposals and will decide the budget allocation (as detailed below). This committee is composed of members of the DRIVE partners who have equal voting rights with a 50/50 parity between public consortium and vaccine companies partners.
3. Final site selection will be determined in an Independent Scientific Committee (ISC) and DRIVE Steering Committee (SC) meeting to share assessments and build consensus for final decision.

The scientific relevance of the proposal for DRIVE pooled analysis will be evaluated by the ISC using the following criteria:

- Scientific relevance for DRIVE:
    - Ability to adhere to DRIVE generic protocols (conventional study design: Test Negative Design (TND), population-based database cohort studies) or level of appropriateness for DRIVE for innovative studies.
    - Reliable brand-specific information and laboratory testing
    - "Poolability" of the data (setting and age groups, minimum variables)
- Sample size (number of LCI cases, per age group – adults and older adults) and vaccine coverage (for target populations in country/region and per vaccine type or brand when available) – evaluation based on data from previous seasons.

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

- For research collaborators who participated to the previous season:
    - Previous season quality of the data; data transfer timelines; relationship of the collaboration (P95 and Fisabio evaluation)
    - Quality of the study conduct and related documentation (QCAC evaluation)
- ISC scientific evaluation and recommendations (as detailed above).

- Ability to fill identified gaps in DRIVE's existing data collection (e.g. brand coverage, strain-specific estimates) and relevance for pooled analysis in DRIVE.
- Whether a collaborator represents a new partner institution/country currently not represented in the DRIVE studies.
- Feasibility of collecting data related to COVID-19 (at minimum testing results for SARS-CoV-2 is required, see application form) .
- Ability to demonstrate Cost-effectiveness / Co-funding / sustainability of the proposal.

The indicative funding range per proposal is 10 000–50 000 EUR for secondary use of already collected data (depending on sample size) and 60 000–300 000 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. There will be a **fixed budget** to cover the study management and staff and a **variable cost** linked to number of SARI and LCI provided to DRIVE dataset. Additional budget could be considered when specific efforts are proposed to collect key optional variables (co-morbidities, detailed vaccination exposure information, COVID-19 related data…). The maximum budget available for all tendered studies in the 2021/22 season is 2 000 000 EUR. DRIVE reserves the right to not award the whole budget.

Given the exceptional circumstances of the 20/21 influenza season, in which low circulation of influenza was observed due to COVID-19 preventive measures (NPIs, lockdown…), **COVID-19 risk mitigation** for budget allocation was implemented. For the 21/22 season, which is also expected to be impacted by the COVID-19, DRIVE requests the study sites to split their budget proposals into fixed and variable costs. On one hand, DRIVE will consider as fixed costs: staff, costs of study and data management, ethics committee fees or travels. On the other hand, the costs of PCRs, subtyping, lab consumables, sample storage and shipping (if necessary) will be considered variable costs. Regardless of the outcome of the 21/22 season, study sites will receive the budget associated to the fixed costs. However, variable costs will be subject to the number of tests done and will be adjusted at the end of the influenza season 21/22.

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 as part of the cost-effectiveness and suitability of the project.

Technical specifications

Scope

The scope of this tender is to assess IVE against LCI, by vaccine brand. Ideally, the assessment should also be specific to influenza type/subtype/lineage/clade, age group, vaccination target- and risk group.
DRIVE will focus on hospital setting and adult/older adult populations, prioritizing the recruitment of sites that fulfill those pre-requisites. Moreover, given the expected impact of the COVID-19 pandemic, DRIVE has decided (advised by EMA and IMI) to adapt DRIVE protocols to assess the impact of COVID-19 on IVE for the next season (2021/2022). Therefore, feasibility of collecting data related to COVID-19 will be positively valued during the site selection process.

- The applicant should propose to conduct the study according to one of the DRIVE generic study protocols (ANNEX 1&2) and may tailor it to the local specificities 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 contributed data will be processed without the involvement of Vaccine companies representatives involved in DRIVE and will under no circumstances be transferred to outside of the DRIVE secured servers.

The **ownership** of the data will remain with the applicant. The applicant will be free to publish their own results (study specific results) separately from the DRIVE pooled analysis. DRIVE funding for primary data collection should be acknowledged as per publication standards and DRIVE should receive the draft version of the pre-submission manuscript for non-binding comments.

Brand-specificity

Availability of vaccine brand information is critical for DRIVE, when vaccine brand information is not registered as part of the dataset in a site, the applicant should specify how the information can be obtained otherwise (e.g. if only a single vaccine brand is used in the area or by phone calls to the General Practitioners or to the Pharmacists to get the brand information per patient or from existing vaccine registries).
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 2021/22 or specify the local bodies holding this information.

Answering data gaps and poolability of the data

DRIVE aims to cover as many influenza vaccine brands marketed as possible, in adults and the older adults as 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 or comprehensively captured by DRIVE studies. It is also essential to comply with the DRIVE "poolability" criteria and a detailed level of data aggregation should be included in the provided call for tenders' template.

COVID-19 additional components

The inclusion of COVID-19 data in DRIVE for the influenza season 2021-22 will be greatly valuable, as COVID-19 is highly expected to impact the IVE studies. DRIVE is not intended to establish a COVID 19 surveillance network, but to study the influence that COVID-19 will have on IVE estimations, for example:

- COVID-19 could be a confounder for the interaction between vaccination for influenza and getting sick with influenza
- Being at risk for COVID-19 could also be associated with at risk for influenza
- There may be differences in care seeking for influenza vs. COVID-19
- Co-circulation influenza/SARS-CoV-2 occurred and, therefore, co-infection may occur and how co-infection affects one's response to vaccine-derived protection for influenza.

Therefore, DRIVE would like to collect additional information about COVID-19. For instance:

- Triage strategy to screen influenza and COVID-19 cases (using systematic simultaneous tests or influenza and SARS-CoV-2 PCRs or other approaches).
- Clinical symptoms data for each of the 2 diseases.
- Relevant co-morbidities that may be informative to further interpret brand-specific IVE and identify risk specific groups for COVID-19.
- Antiviral treatment 2 weeks upfront (treatment for COVID-19 or not) for potential confounders on IVE.
- SARS-CoV-2 testing results (and type of tests).
- COVID-19 vaccination strategy (roll out process, national recommendations, target populations prioritized, start dates of vaccinations, capacity to collect vaccine type- or brand-specific information or alternative ways of recognizing type/brand).
- COVID-19 vaccination status and date(s) of vaccination

More details will be included in DRIVE's 2021/2022 protocol, which will be updated and will describe in more depth the specific COVID-19 components and variables to be explored next season. The protocol will be available in June 2021 and will be circulated to the selected DRIVE sites.

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. Please refer to DRIVE D7.3: Report on feasible, novel and innovative approaches for measuring influenza VE, available on the DRIVE website for more details.

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. If local adaptations are needed these should be explicitly described in the application.

Timelines for the selected proposals
If your proposal is selected, the following timelines apply. The local study protocol (based on a DRIVE generic protocol, which will be updated to include COVID-19 components and will be available in July 2021) should be submitted to DRIVE at the latest by 30th September 2021. Dataset (individual level or aggregated data) should be submitted to DRIVE at the latest by the beginning of May 2022; when applicable, a preliminary dataset for interim analysis should be submitted to DRIVE by the end of January 2022. The local study report should be submitted by May 2022.

Study design & setting

The **study designs** used may include:

- Case-control study using the test-negative design (TND) (Annex 1).
- Cohort study using electronic databases (Annex 2).
- Other study designs, including prospective cohort studies and novel and innovative designs.

The **settings** used to study IVE may include:

- Hospital setting.
- Population-based studies and databases (based on hospital network databases).

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 **laboratory centres** involved in the studies and **performing the influenza tests** 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 and SARS-CoV-2 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.
- It will be positively valued if laboratory centres are also able to detect SARS-CoV-2 by RT-PCR on site or can arrange SARS-CoV-2 sample testing in associated labs not necessarily on site.

OR

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

Ethics

The applicant shall ensure and collect and submit any necessary ethical committee approvals for all study sites in anticipation of the start of the study and before any participants' enrollment. Once approval from the local Ethics Committee is granted, the confirmation will also be submitted to DRIVE (Fisabio). The applicant should be compliant with their ethical and local regulations for the conduct 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. DRIVE D7.1.2 Core protocol for type/brand-specific influenza vaccine effectiveness studies (test-negative design studies)

Available at: https://www.drive-eu.org/wp-content/uploads/2020/09/DRIVE_D7.1.2_Core-protocol-for-test-negative-design-studies.pdf

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

Available at: https://www.drive-eu.org/wp-content/uploads/2018/12/DRIVE_D7.2_Core-protocol-for-population-based-database-cohort-studies_V1.1.pdf

3. Proposal template (available in the present Call for tenders post).