



**DRIVE**

Development of Robust  
and Innovative Vaccine  
Effectiveness

07.05.2020

Call for tenders – 2020/21 influenza season

Measuring brand-specific influenza vaccine  
effectiveness in EU/EEA

## **Tender Specifications**



# DRIVE

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**Acknowledgement.** The DRIVE project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777363, This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.



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# DRIVE

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## About DRIVE

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The Innovative Medicines Initiative 2 Joint Undertaking (IMI JU) project DRIVE (Development of Robust and Innovative Vaccine Effectiveness, [www.drive-eu.org](http://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 (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 equally represented in the DRIVE Steering Committee; however, the IVE studies themselves are led by public institutions and EFPIA have no role in the operations and no decision capacity on the scientific aspects. An Independent Scientific Committee oversees the process to guarantee the scientific integrity of the studies.

An increasing number of sites are joining DRIVE study platform: 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. DRIVE research collaborators contribute by providing data using both test-negative and cohort study designs. The results of DRIVE's previous seasons are available on the [DRIVE website](http://www.drive-eu.org).

In 2020, the DRIVE network aims to continue evolving. 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 is another option to contribute to the project as associate partners (they can join at any moment and share data from their existing surveillance system); please see the [DRIVE website](http://www.drive-eu.org) for more information.

## Background

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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, 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

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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 2020 to 31 June 2021), 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 pooled analysis.

The data collected for DRIVE specific needs/objectives should be provided to P95, via a secured electronic study support application, 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 industry) 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 IMI, and 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:

- Generating 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

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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-COV2 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 focused investment prioritizing adult and older adult populations and hospital settings in order to obtain more reliable IVE data. Accordingly, the annual DRIVE call for tenders has been updated and only studies focused on adult/older adult populations in hospital settings will be included in the selection process. DRIVE is adapting its protocols to the influence of COVID-19 in the next season (2020/2021), as COVID-19 is expected to substantially impact the IVE studies. Therefore, it is requested to the sites to share some COVID-19 related data as a valuable new condition.

## Eligibility criteria

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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

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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 on vaccines registered under national procedures only (in a single country);
- Expected laboratory confirmed influenza (LCI) cases lower than 30 in the upcoming influenza season.

## Tender timelines

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The call initially opened in February and has been updated subsequently to account for EMA and IMI recommendations. Proposals should be submitted at the latest on **May 28<sup>th</sup> 2020** to DRIVE (by email to [info@drive-eu.org](mailto:info@drive-eu.org)). Any questions about DRIVE will be answered at [info@drive-eu.org](mailto: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.

Official responses from DRIVE indicating whether the proposals are selected will be sent to applicants at the latest **during July 2020** 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 2020 and will organise a site visit or/and meeting when appropriate/possible.

## Evaluation and selection

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Proposals will be reviewed in a stepwise approach:

1. The Independent Scientific Committee of DRIVE (ISC) (see [description on DRIVE website](#)) will perform the scientific evaluation of the proposals based on predefined criteria (please see below).
2. The Steering Committee (SC) of DRIVE will make the strategic review of the proposals and will decide the budget allocation (please see 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 EFPIA 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: 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)
- Estimated sample size (number of LCI) and vaccine coverage for VE:
  - Expected number of LCI per age group (focused on adults and older adults)
  - Vaccine coverage for target populations in country/region and per vaccine type or brand when available.

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 evaluation)
  - Quality of the study conduct and related documentation (QCAC evaluation)
- ISC scientific evaluation and recommendations (see above).
- Ability to fill 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.
- The feasibility of collecting data related to SARS-CoV2 will be positively valued but it is not a requirement that will exclude a site during the selection process.
- 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. Additional budget could be considered when specific efforts are proposed to collect COVID-19 or SARS-CoV2 related data (e.g. testings). The maximum budget available for all tendered studies in the 2020/21 season is more than 1 500 000 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 as part of the cost-effectiveness and suitability of the project.



## Technical specifications

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### 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.

In contrast to our previous public calls, DRIVE will focus on hospital setting and adult/older adult populations, prioritizing the recruitment of sites that fulfill those characteristics. Moreover, given the 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 (2020/2021). 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 ownership of the data will remain with the applicant. The contributed data will be processed without the involvement of EFPIA 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, 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).

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 2020/21 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 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.

DRIVE is maintaining a close dialogue with EMA to ensure that the project meets the expectations set in the EMA guidance. Hence the selection of any study proposal could depend on the feedback from EMA at any time.

The applicant should provide their estimation of the expected number of LCI and ILI/SARI for the upcoming season per vaccine type/brand by age group (adult/older adult). 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.

## **COVID-19 additional components**

The inclusion of COVID-19 data in the influenza season 2020-21 may be 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 BSIVE 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
- It is still unknown if co-circulation 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 COVID-19 PCRs or other approaches)
- Variables to distinct clinical symptoms between the 2 diseases
- Death
- Co-morbidities to 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
- COVID-19 testing results (and type of tests).

More details will be included in DRIVE’s 2020/2021 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 July 2020 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 (pdf) 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

A study protocol (based on a DRIVE generic protocol, which will be updated to include COVID-19 components and will be available in July 2020) should be submitted to DRIVE at the latest by 30<sup>th</sup> September 2020. Dataset (individual level or aggregated data) should be submitted to DRIVE at the latest by the beginning of May 2021; when applicable, a preliminary dataset for interim analysis should be submitted to DRIVE by the end of January 2021. The local study report should be submitted by May 2021.

## 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.

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-CoV2 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-CoV2 by RT-PCR on site or can arrange SARS-CoV2 sample testing in associated labs not necessarily on site.

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 in anticipation of the start of the study and before any participants' enrollment. 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.



## References

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## Annexes

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

Available at: [https://www.drive-eu.org/wp-content/uploads/2018/12/DRIVE\\_D7.1\\_Core-protocol-for-test-negative-design-studies\\_1.1.pdf](https://www.drive-eu.org/wp-content/uploads/2018/12/DRIVE_D7.1_Core-protocol-for-test-negative-design-studies_1.1.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](https://www.drive-eu.org/wp-content/uploads/2018/12/DRIVE_D7.2_Core-protocol-for-population-based-database-cohort-studies_V1.1.pdf)



# DRIVE

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### 3. Proposal template

Available at: [http://www.drive-eu.org/wp-content/uploads/2020/02/DRIVE\\_Proposal\\_template\\_2020.docx](http://www.drive-eu.org/wp-content/uploads/2020/02/DRIVE_Proposal_template_2020.docx)