Work package number [9]	WP2	Lead beneficiary [10]	1 - FISABIO
Work package title	Development of study tools		
Start month	1	End month	60

Objectives

In WP2 we will develop tools that will be used in WP7 for the development of protocols and the conduct of studies. After a complete review and discussion of the potential confounders and sources of bias already published, the consortium will develop tools to facilitate the implementation of the studies, such as development of applications to support the studies, i.e. protocol templates, facilitate site selection, informed consent, collect data uniformly, etc.
Guidelines to identify and select study sites with different vaccine types, guidelines for identification of vaccine status and for the feasibility of using laboratory tools, will be developed and evaluated through the different annual studies.
The Consortium will seek input from the EMA and the expertise of EFPIAs is critical for preparing questions and implementation of feedback.

Description of work and role of partners

WP2 - Development of study tools [Months: 1-60]
FISABIO, IRD, P95, UNIFI, SYNAPSE , THL, ISS, SURREY, UCBL, SP, ABBV, SEQIRUS, GSK Bio
The WP Leader will be FISABIO and the WP Co-Coordinator will be GSK.

Task 2.1. Systematic review of the sources of confounding, bias and strategies to manage their impact in influenza vaccine effectiveness studies
Led by GSK
Partners involved: GSK, FISABIO, THL, P95, UNIFI, ISS, SURREY, SEQIRUS, SP (M1-12).

In alignment with task 1.1. we will conduct a systematic literature review of studies that assess epidemiological aspects that affect the results of the influenza vaccine effectiveness with the objective of bias minimization. This task will also align with task 4.1 that will consider the different statistical analysis strategies used.
Different type of instruments will be analysed and reviewed by separate (i.e. independent) reviewers:
• Results of studies using prospective methodology, where we anticipate that the majority will be based on Public Health sentinel networks and some of them from academic institutions.
• Results of studies using electronic health records (EHR), performing retrospective analysis.
• Study protocols, especially those that use methods for rapid assessment of vaccine effectiveness allowing for the monitoring of the benefit-risk profile of newly released influenza vaccines.
• Methodological papers.
The review will permit to identify modifiers and confounding factors (e.g. season, time since vaccination, study site, chronic conditions, etc.) that may bias the results of the studies, and identify actions that could be implemented to decrease bias.
The literature search will be conducted, and data extracted by one investigator and independently reviewed by at least two separate researchers.
An effort to gather even unpublished studies and protocols will be done. Attention will be payed to all PHIs that carry out annual IVE studies and innovative approaches. All results will be discussed among the different stakeholders. Recommendations for IVE studies from ECDC and WHO will also be considered. A report with these systematic reviews will be deliverable 2.2.

Task 2.2: Development of guidelines for the identification of vaccine status and brand in study participants
Co-led by GSK/FISABIO
Partners involved: GSK, FISABIO, IRD, UNIFI, ISS, SURREY, SP (M1-24).

To measure brand-specific vaccine effectiveness, the identification of the type of vaccine used for the identification of vaccine status and brands used at study sites in each age/risk group of patient is crucial. Guidelines to assess the feasibility of using the different existing immunization registries to improve data quality will be developed. Where relevant and agreed, we will share experience acquired in EU/EEA Member States that have initiated immunisation registries and the use of data mining tools. Recommendations on which registries should be implemented to help improving data quality will be made for countries where no registries exist. In addition, the different existing or in development tools for identification of brand, type, batch number, expiring date and other characteristics of

the administered vaccine will be identified and reviewed, such as the immunization information systems, Vaccine Identification Standards Initiative (VISI) and the use of barcodes.
The results of the review will be used to define methodology guidelines for the identification of vaccine status and brands used at the study sites. This will inform the protocol development in WP7.
Input and data collected in task 3.1 may be also be used to develop the guidelines.
This guideline will be deliverable 2.4.

Task 2.3 Review of and guidelines on laboratory tools for influenza virus characterization (genetic, perhaps even whole genome, and antigenic analysis)
Led by UCBL
Partners involved: UCBL, FISABIO, SEQIRUS, GSK, SP (M1-60).

Based in the current WHO/ECDC recommendations for influenza virus characterization, feasibility of the incorporation of laboratory tools (e.g. RT-PCR for influenza screening, hemagglutinin/neuraminidase and whole-genome influenza virus sequencing for molecular epidemiology) will be assessed. The related recommendations (deliverable 2.6) will inform WP7. Virological analysis will be performed locally. These virological analysis will include influenza screening and molecular epidemiology as described in WHO recommendations:
RT-PCR for influenza screening is the current gold-standard technique for influenza A and B detection and strain genotyping. Hemagglutinin (HA)/neuraminidase (NA) and whole-genome influenza virus sequencing for molecular epidemiology, as described in the WHO recommendations in vaccine efficacy studies. Next-generation sequencing (NGS) offers significant imprvements in speed and outputs. NGS allows the identification of several SNPs associated with enhanced replication, and minor antigenic variants which may impact antibody recognition. Guidelines on the use of these molecular assays and protocols for test-negative IVE studies will be developed.
In case that further virological analysis be considered for a deeper research in the relationship between virus/host/vaccine, and these cannot be performed at the national laboratories, a selection of samples from different sites will be sent to the central DRIVE laboratories (UCBL and FISABIO).

Task 2.4: Development of the Standard Operating Procedures (SOPs) based on the core protocols
Co-led by SURREY/GSK
Partners involved: SURREY, UCBL, THL, SEQIRUS, GSK, SP (M1-60)

In order to harmonize the approach to implement the protocols in the study sites, standard operating procedures will be developed. The SOPs will encompass several elements that would enable to define the overall approach to follow to comply with the Good Pharmacovigilance Practice and will ensure quality of data generated. SOPs will encompass but will not be limited to the definition of the format and content guidance of the study protocol, the SAP, tables, figures and listings, study report, analysis report, the procedures for the collection, management and reporting of safety data (if applicable). The detailed approach to ensure that the data privacy is handled appropriately and management of both sensitive and non-sensitive Personally Identifiable Information (PII), transfer of data using a secured and auditable pathway and storage policy.
The content of the SOPs will be defined in detail and be aligned with local regulation, GVP and/or other relevant guidelines. The developed SOPs will be deliverable 2.1.

Task 2.5: Develop sampling schemes and sample size needed.
Co-led by P95/GSK
Partners involved: P95, FISABIO, UNIFI, ISS, SP, ABBOTT, GSK (M6-12).

To measure brand specific VE, the seasonal sample size should be large enough to conduct stratified analysis (e.g. by age group and strain). Sample size is a key element to define the feasibility of measuring product-specific influenza VE. Data collected in task 3.1 will feed into the sampling scheme development.
The minimum sample size will be estimated for each study to obtain precise VE estimates. However, pooled analyses will also be conducted to increase the power of individual studies and thus allowing to explore additional stratifications, analysis with further granularity into age groups or risk groups. A minimum of laboratory-confirmed cases will be determined a priori to ensure the precision of the results. The results of this WP will be incorporated into the different protocols.

Task 2.6: Development of an electronic study support application.
Co-led by P95/FISABIO
Partners involved: FISABIO, P95, UNIFI, SURREY, UCBL, THL, GSK, SP (M1-60).

Complying with Good Epidemiological Practice (GEP), we will develop an electronic study support application to be used for multiple purposes that will ease the day to day work of the whole project, including the studies. The main objective of the application will be to build an inventory of study sites to serve as a basis for the annual study tenders

(Task 2.7). For this purpose, the application will be designed to collect essential data to characterize the sites, including capacities, experience over the years, vaccines used in previous or years and where known in the upcoming season, as well as the feasibility to share data with DRIVE.
The application will also facilitate the data collection regarding quality and feasibility criteria (Task 3.3) from the sites.
The electronic tool application may be extended for study data collection. Given however the different national requirements, the different sources of data (primary or secondary) and the expected difficulty in attaining a unique harmonized data collection system, it is expected that most of the study data will be collected, aggregated and analyzed first at a local level using existing means and modes of data collection. The functionality of collecting VE study data through this electronic application may however be found very suitable for novel approaches to IVE studies.
All data will be stored on secure single user-friendly data platform(s), as allowed by Member States' laws; and different levels of access to the application will be defined for each interested stakeholder, also promoting transparency. Where possible this will use the same infrastructure developed in Task 4.2.2 for the central receipt of the VE study data, particularly if the study data collection become a functionality of this study support tool. This will be deliverable 2.3.

Task 2.7: Development of conditional annual study tenders for influenza vaccine effectiveness study conduct.
Co-led by FISABIO/GSK
Partners involved: FISABIO, SYNAPSE, SEQIRUS, GSK, SP (M1-52).

The ability to cover all available brands will depend on the ability to target sites where specific brands are available or alternatively to capture a large enough sample with sufficient geographic coverage. Site selection is an essential part of this. However, site selection is a multi-factorial process. Beyond specific vaccine brand use, the characteristics of the underlying population, eligibility criteria (such as available capacity, previous experience or quality indicators or ability to share data) are among the basic characteristics to consider when evaluating sites.
Using the application tool developed in Task 2.6, DRIVE will provide a pan-European inventory of sites considering all these site characteristics collectively.
The starting point for the annual study tender process is the expected distribution of the vaccine brands throughout Europe identified in Task 3.1. Considering the data required for an IVE by type/brand, and depending on this expected distribution of the vaccine brands, DRIVE will release annual study tenders to fill data gaps and select/contract sites able to conduct influenza vaccine effectiveness studies. The study tenders will consider study site criteria, population selection criteria, geographical criteria, population size, and overlay this information each year with the expected influenza vaccine brand use in the next season to generate a list of potential study sites to approach for participation.
These tenders will allow to achieve the sample size and vaccine brand coverage needed (estimated in T2.7) and ensure representativeness of the influenza virus circulation in EU, as the strains that circulate may be different across EU and present different levels of matching with the vaccine. Initially defined site selection criteria in this task may need to be adapted following the learnings of the quality and feasibility assessments from Task 3.3 and also the study results. This iterative process will additionally ensure that participating sites have been shown to actually meet certain quality standards and were able to contribute timely and complete data.
Annual study tenders, that will follow all technical and legal requirements, will be deliverable 2.5. These study tenders will be released by FISABIO, and the agreement will be signed among FISABIO and the selected institutions. DRIVE seeks to collaborate with the PHIs in Europe, and will encourage them to provide data. Tenders will have this into account. In case that there is no or limited data available from PHIs or in an area of interest (a specific vaccine brand is used), DRIVE will engage academia, local health authorities' teams or other clinical networks able to perform the studies.
The successful performance of this task will allow DRIVE-PHIs to be in line, and will suppose a substantial contribution to the sustainability to the European platform as envisaged by DRIVE.
There is a budget of 5,057,500€ for the studies, and that will include the costs of providing of data to DRIVE. The budget will be invested with a small amount on the POC study and with a progressive increase over the 4 study years. The budget allocation will be based on different factors:
• Type of data provided: population databases, prospectively collected clinical data or other.
• Type of infrastructure established surveillance systems either ambulatory or hospital based, or new study sites developed in collaboration with DRIVE to obtain results from areas that are interesting for the project and have no studies established.
• The sample size provided.

Participation per Partner

Partner number and short name	WP2 effort
1 - FISABIO	14.10
2 - IRD	1.00
3 - P95	10.00
4 - UNIFI	6.00
5 - SYNAPSE	7.70
6 - THL	4.00
7 - ISS	7.00
8 - SURREY	6.00
10 - UCBL	13.00
12 - SP	3.00
13 - ABBV	2.50
14 - SEQIRUS	1.50
15 - GSK Bio	4.00
Total	79.80

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D2.1	Standard Operating Procedures (SOPs) and templates	8 - SURREY	Report	Public	8
D2.2	Report of the results of a systematic analysis on existing initiatives, tools, and/or study protocols for determining IVE […]	15 - GSK Bio	Report	Public	12
D2.3	Electronic study support application	3 - P95	Websites, patents filling, etc.	Public	12
D2.4	Guideline for the identification of vaccine status and vaccine used in study participants	15 - GSK Bio	Report	Public	16
D2.5	Annual tender for influenza vaccine effectiveness study conduct	1 - FISABIO	Report	Public	16
D2.6	Recommendations for virological analysis of samples of the studies	10 - UCBL	Report	Public	30

Description of deliverables

D2.1. Standard Operating Procedures (SOPs) and templates (M8, annual updates);
D2.2. Report of the results of a systematic analysis on existing initiatives, tools, and/or study protocols for determining IVE and results of a systematic review of the literature to identify and analyse the main confounding factors in IVE studies (M12);
D2.3. Electronic study support application. (M12);
D2.4. Guideline for the identification of vaccine status and vaccine used in study sites (M16, periodic updates);
D2.5. Annual tenders for influenza vaccine effectiveness study conduct (M16, updates on M28, M40);
D2.6. Recommendations for virological analysis of samples of the studies (M30).

D2.1 : Standard Operating Procedures (SOPs) and templates [8]

Deliverables co-led by SURREY and GSK. It will be submmited in month 8 and annually updated.

D2.2 : Report of the results of a systematic analysis on existing initiatives, tools, and/or study protocols for determining IVE […] [12]

Lead participants of this report will be FISABIO and GSK.

D2.3 : Electronic study support application [12]

Lead participants of this delivable will also be FISABIO and GSK

D2.4 : Guideline for the identification of vaccine status and vaccine used in study participants [16]

This deliverable will be co-led by FISABIO and GSK. It will be submmitted in M16 and will have periodic updates.

D2.5 : Annual tender for influenza vaccine effectiveness study conduct [16]

This report will be led by FISABIO and GSK, submmitted in M16 and updated on M28 and M40

D2.6 : Recommendations for virological analysis of samples of the studies [30]

This deliverable will be co-led by UCBL and SEQIRUS.

Schedule of relevant Milestones

Milestone number[18]	**Milestone title**	**Lead beneficiary**	**Due Date (in months)**	**Means of verification**
MS4	Complete the systematic review with recommendations for protocol development	15 - GSK Bio	12	Deliverable 2.2 submitted.
MS5	First version of the study support tool released	3 - P95	12	Milestone co-led by P95 and FISABIO. Deliverable 2.3 submitted.
MS6	First version of guidelines for the identification of vaccine status and vaccine use in study participants released	15 - GSK Bio	16	Mileston co-led by GSK and FISABIO. Deliverable 2.4 submitted.
MS7	First study tender launched	1 - FISABIO	16	Milestone co-led by FISABIO and GSK. The mean of verification will be the publication of the study tender.