Work package number [9]	WP4	Lead beneficiary [10]	3 - P95
Work package title	Framework for analysis and study reports		
Start month	1	End month	60

Objectives

To create a model to analyse, present, interpret and report influenza VE study results in such a way that all stakeholders can endorse its conclusions.

Description of work and role of partners

WP4 - Framework for analysis and study reports [Months: 1-60]
P95, FISABIO, UNIFI, THL, ISS, SURREY, UCBL, IABS-EU, SP, ABBV, SEQIRUS, GSK Bio
The WP Lead will be P95 and the WP Co-Coordinator will be ABBOTT.

Task 4.1: Analytical methods.
Partners involved: P95 (Task leader), UNIFI, THL, ISS, SEQIRUS, SP, ABBOTT, GSK(M4-55).

Create a standard set of analytical methods that can be applied to measure VE in the European context of diverse vaccine manufacturing, distribution, and administration as well as diverse influenza diagnostic and therapeutic approaches. This set of methods will build upon existing guidance documents made available by the ECDC and be linked with tools developed in WP2. Specifically, we will build on the work carried out by EpiConcept on behalf of ECDC in the 2008 report "Methods for measuring influenza vaccine effectiveness during influenza seasons and pandemics in the European Union". We propose to update and expand this report in order to build the interim methodological guidelines to be used during season 2017-2018, with annual updates based on the input and feedback from WP7 and WP2. These methodological guidelines (deliverable 4.1) should address the following:
• The challenges posed by pooling estimates from different data sources
• The challenges posed by standardising analyses across different countries and data sources
• The challenges posed by the potential biases and confounders expected across the different settings
• Methods for rapid assessment of vaccine effectiveness allowing for the monitoring of the benefit-risk profile of newly released influenza vaccines
• Optimization of the value of microbiological and virological information.
P95 will lead the task and develop the draft deliverable 4.1. All partners will provide feedback on the draft deliverable. In particular, UNIFI will provide expertise on the optimization of the value of microbiological and virological information, THL on the methods for rapid assessment of vaccine effectiveness and the industry partners on the challenges posed by pooling data, standardising analysis and potential biases and confounders.

Task 4.2: Data management, analysis and interpretation tools
Partners involved: P95 (Task leader), FISABIO, UNIFI, ISS, THL, UCBL, SP, ABBOTT, GSK (M8-60).

Task 4.2.1: Develop a generic Data Management Plan (DMP). Data to be analysed for influenza VE purposes will be collected at different sites across Europe. Some level of integration of these data in a centralised fashion will be needed to ensure sufficiently powered brand specific analyses. The modes and extent of such integration will need to be agreed with the local study sites and be dependent on the possibility of harmonizing data collection across sites as well as transfer of data across geographical borders. The details of such harmonization will be described in a DMP, which will develop throughout the course of the project as experience is gained and regulations adapted. Important in this perspective will be the integration of the new European national regulations across the EU. The DMP will first describe the minimum data requirements (MDR). This will allow to carry out early comparison of aggregated data, that will ensure that there will be much less scope for incompatible data in the final studies. The DMP will be reviewed based on the feedback from other tasks in this WP as well as WP2. The generic DMP will be deliverable 4.2.(updated on D4.8 and D4.9).

Task 4.2.2: Set up the necessary infrastructure for data collection and analysis for the pooled analysis. This task will take place primarily during the first year of the project, and will involve setting up a secure server environment where data collected at individual study sites can be received to be analyses in a pooled fashion. This environment will be conformed to the DMP, where the data requirements for collection and transfer for the pooled analysis will be outlined. We will develop a secure central data management system in Belgium. P95 will adapt and scale its existing central Database Analysis Center (DAC) infrastructure, hosted at a trusted third party Custodix, to receive the locally collected and aggregated data in a securely and remotely accessible central DRIVE storage and processing server through encrypted

individual user-based authentication. The Custodix environment and expertise has been used in implementing in other IMI projects such as EHR4CR and EMIF. The description and technical specifications of the infrastructure to centrally receive and analyse data will be deliverable 4.5.

Task 4.2.3: Develop a generic statistical analysis plan (SAP) that can meet the need for rapid VE assessment as well as the need for transparency and auditability. The development of a generic SAP that can be adapted to suit different study designs as per the methodological guidelines developed in task 4.1, and aligned with the tools development in WP2. The analytical plan should at minimum address the requests of the EMA guidance, but equally foresee answers to several scientific questions in the influenza field, such as influenza type specific VE, age and risk-group specific VE, duration of VE (within and between seasons), VE for different clinical endpoints and different severity levels, in line with the needs of all stakeholders as will be defined in WP1 (Task 1.1). The generic SAP will be deliverable 4.4. and will be the basis for the study SAPs which will be developed by WP7.

Task 4.2.4: Develop a set of considerations for the interpretation of VE data. The interpretation rules will be aligned with existing guidance such as ENCEPP guidelines and guidelines under development in the IMI ADVANCE project. Careful consideration will be put on sample size requirement for generating robust conclusions. Interpretation will not only focus on effectiveness but also aim to integrate VE results with Hemagglutinin/neuraminidase and whole-genome influenza virus sequencing for molecular epidemiology and characterization of strains identified in vaccinated individuals, as compared to those identified in non-vaccinated controls. Ideally, IVE studies should produce antigen-specific (strain/clade-specific/B-lineage) data. These deliverables could be used to feed the WHO vaccine strain selection mechanism, the EU Influenza surveillance network (EISN) and the WHO Global Influenza Surveillance & Response systems (GISRS). These deliverables are linked to WP2 (Tools and protocols development) and WP7 (Pilot studies). Interpretation will also consider the need to communicate with stakeholders besides regulators, public health and manufacturers such as the general public, patient or consumer groups, as further defined in WP5.
P95 will lead this task (4.2), and take the lead for sub-tasks 4.2.1, 4.2.2. and 4.2.3. FISABIO will provide expertise on data management (4.2.1), analysis (4.2.3) and interpretation of VE data (4.2.4), and lead sub-task 4.2.4. UNIFI, ISS, THL and UCBL will provide expertise on the analysis (4.2.3) and interpretation of VE data (4.2.4). Industry partners will provide expertise on all sub-tasks.

Task 4.3: Report template
Partners involved: ISS (Task leader), FISABIO, P95, UNIFI, THL, SEQIRUS, SP, ABBOTT, GSK (M10-54).

Based upon the toolset, analytical and interpretation guidelines, we will develop VE studies report templates. These templates will need to be in line with the communication requirements as stipulated in WP5 and regulatory guidelines. Separate sections will address stakeholder specific needs (e.g. EMA, PHIs and general public). The template will be used for the study-specific reports which are written by WP7. These templates will be D4.3 and will be updated annually based on feedback from WP7, WP3 and WP5.
ISS will lead this task. FISABIO, P95, UNIFI and THL will provide expertise in VE report development. FISABIO, THL and ISS will provide input on addressing the needs of NPHI. Industry partners will provide expertise in report development and provide input on addressing regulatory requirements.

Task 4.4: Alignment with regulatory requirements
Partners involved: IABS-EU (Task leader), UNIFI, THL, SEQIRUS, SP, ABBOTT, GSK (M1-60).

To ensure the alignment of the planned analyses and reports with the regulatory requirements as stipulated in the EMA guidelines, the planned studies, analyses and reports will be steered accordingly, scientific advices will be requested from EMA or other regulatory agencies based on the first interim report detailing how the VE study results could fulfil the new EMA requirements. Through an iterative process, EMA inputs will be included in subsequent reports. The EFPIA members will be actively involved in preparing the submission package.
More concretely, under the leadership of WP4 leader, IABS-EU, together with regulatory experts of EFPIA partners, will work closely with all work packages to ensure that, from start, studies and protocols always anticipate answers to the expectations of regulators. In particular, the planned studies of WP7 will be discussed between WP4 partners and WP7. Where needed, IABS-EU will outreach to regulatory agencies to validate, as much as possible, that the studies will answer regulatory concerns. The same will be done on the governance model (WP1) to ensure that the model copes with regulatory aspects on vaccine efficiency. Lessons learned from ADVANCE will be helpful. The electronic support system (WP2) will receive regulatory input to ensure traceability for regulators concerning vaccine efficacy.
IABS-EU will ensure input from all work packages from start as a key factor for success. This will be done through regular contacts and conferences with all work packages. A report of these meetings will be available to all concerned. The “regulatory” group will be composed of at least one representative of each work package to ensure regulatory streamlining over the whole project (transversability). It will ensure balanced representation of epidemiologists, researchers and regulators from both public institutions and EFPIA members.

As it does in IMI projects ZAPI and VAC2VAC, IABS-EU will, in complete consensus with the regulatory group, reach out to regulatory agencies for consultation on protocols, results and regulatory processes to be adapted or not. It will also reach out to WHO, ECDC and other international and global organisations where needed.
IABS-EU will lead this task and be overall responsible for D4.7, providing independent regulatory expertise. UNIFI and THL will provide regulatory input from the academic and public perspective, while EFPIA partners will provide regulatory expertise and input from the industry perspective.

Participation per Partner

Partner number and short name	WP4 effort
1 - FISABIO	6.50
3 - P95	15.00
4 - UNIFI	10.40
6 - THL	6.00
7 - ISS	8.00
8 - SURREY	5.60
10 - UCBL	5.00
11 - IABS-EU	12.90
12 - SP	3.00
13 - ABBV	9.80
14 - SEQIRUS	1.50
15 - GSK Bio	1.03
Total	84.73

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D4.1	Methodology guidelines for concerted analysis of data and control of confounding factors	3 - P95	Report	Public	4
D4.2	Generic DMP	3 - P95	Report	Public	6
D4.3	Report templates	7 - ISS	Report	Public	8
D4.4	Generic SAP	3 - P95	Report	Public	9
D4.5	IT infrastructure to receive and analyse the data	3 - P95	Websites, patents filling, etc.	Public	12
D4.6	Points to consider document on the interpretation of VE results	1 - FISABIO	Report	Public	12

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D4.7	Evaluation reports of how the vaccine effectiveness results could fulfil the new regulatory requirements	11 - IABS-EU	Report	Public	15
D4.8	Mid-Term DMP	3 - P95	Report	Public	30
D4.9	Final DMP	3 - P95	Report	Public	60

Description of deliverables

D4.1. Methodology guidelines for concerted analysis of data and control of confounding factors (M4 first version, M55 final version);
D4.2. Generic DMP (first version) (M6);
D4.3. Report templates (M8 first version, M15, M27, M39 annual review, M59 final version);
D4.4. Generic SAP (M9);
D4.5. IT infrastructure to receive and analyse the data (M12);
D4.6. Points to consider document on the interpretation of VE results (M12 Updates annually);
D4.7. Evaluation reports of how the vaccine effectiveness results could fulfil the new regulatory requirements (M15, annually updates);
D4.8. Mid-Term DMP (M30)
D4.9. FInal DMP (M60)

D4.1 : Methodology guidelines for concerted analysis of data and control of confounding factors [4]

This report will be led by P95 together ABBOT. It will be submmitted in M4 and updated on M55.

D4.2 : Generic DMP [6]

This deliverables will be co-led by P95 and ABBOT. It will be submmitted in M6 and updated on M30 and M60 (separate deliverables).

D4.3 : Report templates [8]

This report will be led by P95 and ABBOT, submmitted in M8 periodically updated in M15, M27, M39 and M59.

D4.4 : Generic SAP [9]

This deliverables will be led by P95 and ABBOT.

D4.5 : IT infrastructure to receive and analyse the data [12]

This deliverables will be led by P95.

D4.6 : Points to consider document on the interpretation of VE results [12]

This report will also be co-led by P95 and ABBOT, submmitted in M12 annually updated.

D4.7 : Evaluation reports of how the vaccine effectiveness results could fulfil the new regulatory requirements [15]

The lead beneficiaries of this deliverable will be IABS-EU and SEQIRUS. It will be delivered in M15 and annually updated.

D4.8 : Mid-Term DMP [30]

Mid-term update of D4.2

D4.9 : Final DMP [60]

Final update of D4.2

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS12	Methodology guidelines agreed and completed (first version)	3 - P95	7	Milestone co-led by P95 and ABBOTT. Deliverable 4.1 submitted.
MS13	Generic DMP (first version) completed	3 - P95	6	Milestone co-led by P95 and ABBOTT. Deliverable 4.2 submitted.
MS14	IT infrastructure completed	3 - P95	12	Milestone co-led by P95 and ABBOTT. Deliverable 4.5 submitted.
MS15	Generic SAP (first version) completed	3 - P95	9	Milestone co-led by P95 and ABBOTT. Deliverable 4.4 submmitted.
MS16	Document interpretation of VE results (first version) completed	1 - FISABIO	12	Milestone co-led by P95 and ABBOTT. Deliverable 4.6 submitted.
MS17	Report templates produced (first version)	7 - ISS	8	Milestone co-led by ISS and ABBOTT. Deliverable 4.3 submmitted.
MS18	Evaluation reports VE fulfilment of regulatory requirements completed	11 - IABS-EU	15	Milestone co-led by ISS and ABBOTT. Deliverable 4.7 submitted.