1.3.3. WT3 Work package descriptions

Work package number [9]	WP1	**Lead beneficiary** [10]	2 - IRD
Work package title	Development of a governance model for joint influenza vaccine effectiveness studies in Europe		
Start month	1	**End month**	60

Objectives

To reach consensus on an acceptable governance model that will allow the different stakeholders to sustainably fulfil their respective missions and obligations from evidence generated by seasonal influenza vaccines effectiveness studies in Europe.

Description of work and role of partners

WP1 - Development of a governance model for joint influenza vaccine effectiveness studies in Europe [Months: 1-60]
IRD, FISABIO, P95, UNIFI, THL, ISS, COMO, IABS-EU, SP, SEQIRUS, GSK Bio
The WP leader will be IRD and the WP Co-Coordinator will be SP.

The objective of the work package 1 (WP1) is to build on a multi-stakeholders IVE agenda which will support the consensus building around the governance of the DRIVE platform among the different stakeholders, allowing and encouraging them to participate. The work has been organised in three tasks. The first task will be to set up this agenda. The second task will be to fine tune the governance of the platform, ensuring at the same time an active stakeholders engagement. The third task will propose a generic development plan for Influenza vaccines effectiveness, which would benefit from the established infrastructure.

Task 1.1: Multi stakeholder IVE Research Agenda
Partners involved: IRD (Task leader), SP, all (M1-60)

Vaccine effectiveness is a classical component of vaccine programmes monitoring and evaluation, which is a public health mandate. Vaccine effectiveness estimates are requested from Industry by regulatory authorities to monitor the benefit/risk (B/R) of their vaccines, inducing responsibilities to Market Authorization Holders (MAH). This B/R monitoring is of paramount importance for newly registered vaccines for which the real-life performance is unknown (HPV, Dengue) but it is also more and more requested for older vaccines, in particular those where effectiveness is expected to vary depending on the context of the program implementation (influenza, pertussis). Specifically, for seasonal Influenza vaccines, the recent EMA Flu guidelines replaced the request for yearly immunogenicity clinical trials by the generation of brand specific vaccine effectiveness , as well as earlier guidance on safety monitoring. The convergence of the interests of different stakeholders provides opportunities to share resources and knowledge, provided barriers (mostly the fear of conflict of interest from the manufacturers) are alleviated on an appropriate way.

1.1.1. A first step in this task will be to identify a common research agenda for the different stakeholders at EU/EEA and national level i.e. ECDC, EMA, national public health institutes (NPHIs), supranational bodies such as WHO, national regulatory agencies (NRAs), HTA and recommendation bodies, vaccine manufacturers, health care professionals (HCPs), patients and academia.
This agenda will be based on a systematic analysis of the evidence needed, its availability and quality, taking into account activities developed by concurrent programmes (as described in section 1.3.3), and seeking contribution from these initiatives (see task 5.7). This analysis will be based on a framework, to be further developed, adapted from previous work and will consider all the ongoing research questions e.g. effect of previous vaccination, immunoscenescence, waning immunity, virus drift, indirect protection) but classifying these gaps into categories (e.g. impact of manufacturing, administration, host environmental, and study design). Given the importance of regulatory aspects in the DRIVE project, a systematic analysis of specificities of estimation of Brand Specific Influenza Vaccine Effectiveness (BSIVE) compared to Influenza Vaccine Effectiveness in general (IVE) will be performed.
These categories will facilitate identification of contributing stakeholders; This identification should make complementarity of stakeholders explicit, and be a rational for collaborations. It will also provide a basis for prioritization of activities, their feasibility, and evaluation of expectations.

Analysis of published (peer reviewed and reports) work as well as non-published works will contribute to the elaboration of this multi-stakeholder agenda. This will be deliverable 1.1 (M10). This deliverable will be presented, discussed and refined during a dedicated workshop open to external stakeholders.
Focus will be put on factors that may increase the quality level from observational studies (as defined by the GRADE system). Similar approaches have been taken for vaccines in general and for HTA evaluation . DRIVE will further investigate these approaches with a focus in the regulatory field of IVE and identifying ways to increase the quality of the data aiming at reducing uncertainties, allowing to use simpler methods and analyses, preventing or minimizing risk of biases. The agenda will highlight evidence available for action, gaps and priorities, synergies and complementarities, and express the needs and expectations from different stakeholders.

See Figure 4 in Annex I of the DoA. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) for Systematic Reviews

1.1.2 The initial agenda should be periodically updated, accounting for DRIVE WPs production and based on lessons learned, interfacing with other initiatives and integrating scientific advances. The process of joint elaboration and updating of a plan to answer each stakeholder's needs will create commonality of interest and set the ground for the collaboration. Subsequent updated plans will be performed in M24, M48 and M60.
IRD will lead this task and propose the framework for the systematic analysis, that will be adopted after contribution from all partners. IRD will lead the systematic analysis conducted by a core group from all workpackages. CoMo, as patient organisation, will contribute to the research agenda on the perception of partnerships and associated risks on scientific independence, and related aspects of communication, that could be identified in WP5. EFPIA partners will contribute through their vaccines study implementation expertise, quality processes requirements and regulatory interactions experience. Input from the external consultation will be incorporated in the research agenda by the core group.

Task 1.2: Set up of an acceptable governance for collaborative studies and stakeholders engagement
Partners involved: SP and IRD (Task leaders), all (M1-60)

A model for studies has been identified during stage 2 preparation of the proposal with intensive input with ECDC. DRIVE partners agreed to start with this model and further elaborate during the project, based on available governance principles, models and input from ECDC and PHIs.

See Figure 5 in Annex I of the DoA. Starting DRIVE platform governance for collaborative studies on IVE, to be piloted and updated.

In this model, EFPIA will have the opportunity to fulfil their regulatory requirements (accountability for data quality and accuracy of the analysis plan, data analysis and interpretation), preserving at the same time the independence of the study by having only an indirect involvement: (i) study and data quality assessment is performed by a group of stakeholder involving EFPIA representatives without possibility to impact on the data collection or the study (auditing mechanism), (ii) Review of the protocol, analysis plan, results and interpretation is facilitated through written comments to an independent scientific committee, (iii) funding is performed through a trustee.
A comprehensive and detailed report on the Governance Standard Operating Procedures (SOP) will be developed at the start of the project (D1.2 in M3) to clarify all decision-making processes, focusing on scientific independence and transparency. These SOPs will follow governance principles reflecting scientific independence, regulatory, ethical or legislative constraints, with the aim to cover all stakeholders' needs. These SOPs will follow a developing procedure, taking into consideration all stakeholders needs. In this first version of the SOPs, we will further develop the criteria for the evaluation of the Mid-Term review and the decision by IMI of the on-going of the project. This model will already be based on the lessons learnt from ADVANCE project WP1 and its evaluation in ADVANCE WP7. Outcomes from the workshop: ADVANCE Public-private collaborations for vaccine benefit-risk monitoring in Europe: the ADVANCE framework and governance principles March 23,24 2017, EMA office, London will also be incorporated. The increase of the number of Public Health Centres participating in the project for the estimation of the effectiveness of a higher number of brands will be one of the most important criteria to take into account.
In order to assess the course of the project, the acceptance of the governance model and the state of the evaluation criteria, the compliance and implementation of the SOP will be monitored by the QCAC, updated and reported in M22 (D1.5). The final decision of go/no go of DRIVE will depend on the decision by IMI following the recommendation by independent experts at the M24 review. Deliverable 1.5 at month 22 will summarize the state of the project that may help experts for the technical audit in M24 (MS2).

Focus will be on the operationalization and adaption of the generic models proposed by ADVANCE by conducting several extensive consultations with key stakeholders. These stakeholders' consultations will provide opportunities to educate, alleviate concerns and build consensus and become the backbone of our stakeholder engagement strategy. As a follow-up, specific face to face meeting will be organized with main PHIs to better understand their concerns and propose

tailored solutions that could be piloted during the course of the project. ECDC, EMA and WHO will also be involved in these discussions. The elaboration of the list of governance principles will also be conducted through exchanges at professional societies level. It will be promoted as a topic of interest in the special interest group on vaccines from the International society of pharmacoepidemiology (VAXSIG vaccines from ISPE), and ideally reflected in the GPEP, as well as at International Epidemiological association (IEA) and its related Good Epidemiological practices. Systematic analysis of national epidemiological unions and related codes will be performed (e.g. ADELF code of deontology for French speaking epidemiologists).

The evolution of the starting model, together with the perception assessment captured by the communication work package (WP5), will be translated into deliverable 1.3 (M60) which will describe the final governance principles and proposal. SP who already lead the governance workstream from the ADVANCE project will lead this task together with IRD. Strong synergies between the more theoretical ADVANCE governance models and DRIVE proof of concepts are anticipated.

Task 1.3: Develop an overall complete post authorisation development plan for seasonal influenza vaccines effectiveness in the EU/EEA
Partners involved: IRD (Task leader), SP, all (M48-60)

In this framework, deliverable 1.4 (M60) will adapt the results of task 1 and task 2 toward a proposal for a generic post authorisation development plan that will allow to provide critical information for sustainability (platform, possibility of network evolution, regulatory aspects, costs and funding mechanisms).
This generic plan will also inform on European possibilities for monitoring effectiveness for the next generation of influenza vaccines.
Providing insurance that post authorisation vaccine effectiveness of a specific vaccine can be estimated in Europe, and how, is likely to accelerate early phases, facilitate registration and better evaluate the added value of the new vaccines for the ultimate benefit of EU/EEA citizens. Furthermore, this could be extended to other vaccines, as expected in the JIVES call, with adaptations and hopefully simplifications, as seasonal influenza vaccines effectiveness's are not the simplest to monitor.
IRD will lead this task with input from core group of task 1.1 and lead from task 1.2

Participation per Partner

Partner number and short name	WP1 effort
1 - FISABIO	9.60
2 - IRD	14.40
3 - P95	6.00
4 - UNIFI	4.80
6 - THL	6.00
7 - ISS	8.60
9 - COMO	9.60
11 - IABS-EU	9.60
12 - SP	3.00
14 - SEQIRUS	0.50
15 - GSK Bio	0.53
Total	72.63

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D1.1	Multi Stake-holder Research Agenda	2 - IRD	Report	Public	10
D1.2	Governance Standard Operating Procedures (SOP)	12 - SP	Report	Public	3
D1.3	Final report on governance and principles	12 - SP	Report	Public	60
D1.4	Generic post authorisation development plan on effectiveness of vaccines	2 - IRD	Report	Public	60
D1.5	Report on the Governance SOP implementation	2 - IRD	Report	Public	22

Description of deliverables

D1.1. Multi-stakeholder research agenda (M10 and updated plans annually).
D1.2. Governance Standard Operating Procedures (SOP) (M3);
D1.3. Final report on governance and principles (M60).
D1.4. Generic post authorisation development plan on effectiveness of vaccines (M60).
D1.5. Report on the Governance SOP implementation (M22).

D1.1 : Multi Stake-holder Research Agenda [10]

This deliverable will be co-led by IRD and SP. It will be submmitted in M10 and annually updated.

D1.2 : Governance Standard Operating Procedures (SOP) [3]

This report will be co-led by IRD and SP. It will be submmitted in M3

D1.3 : Final report on governance and principles [60]

This deliverables will be co-led by IRD and SP. Final report on governance and principles

D1.4 : Generic post authorisation development plan on effectiveness of vaccines [60]

This deliverable sill be co-led by IRD and SP. Generic post authorisation development plan on effectiveness of vaccines

D1.5 : Report on the Governance SOP implementation [22]

Report on the implementation of D1.2 co-led by IRD and SP

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS1	Workshop open to external stakeholders to discuss the research agenda	2 - IRD	12	Milestone co-led by IRD and SP. It will be verified by the meeting report.
MS2	IMI 2 years-technical audit	1 - FISABIO	24	Milestone co-led by FISABIO and SP as project

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
				leads. Its verification will be done through the submission of D1.5 (report on the governance SOP implementation) in M22
MS3	Final report on governance accepted by all stakeholders	12 - SP	60	Milestone co-led by IRD and SP. Deliverable 1.3 submitted.