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Development of Robust and Innovative Vaccine Effectiveness

WP1 – Governance

D1.3 Final report on governance and principles

Lead contributor	Laurence Torcel-Pagnon (12 – Sanofi Pasteur)
Other contributors	Alexandre Descamps (2 – INSERM) Toni Carmona and Javier Diez Domingo (1 – FISABIO) Sam Nye and Nadia Vaenerberg (9 – CoMO) Gael Dos Santos and Vincent Bauchau (15 – GSK) Hanna Nohynek and Ritva Syrjanen (6 – THL) Roberto Bonaiuti (4 – UNIFI) Mendel Haag (14 – SEQIRUS) Samy Chellali and Angelique Castillo (12 – Sanofi Pasteur) Anke Stuurman and Tom de Smedt (4 – P95) Pieter Neels and Joris Vandeputte (11 – IABS-EU)

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Abstract

The Development of Robust and Innovative Effectiveness (DRIVE) project was set up in July 2017 to address the challenge of brand-specific influenza vaccine effectiveness (IVE) evaluation in the Europe through a Public-Private Partnership (PPP). The DRIVE project included, along 5 years, 16 partners from seven European countries, coming from Public Health Institutes, universities, research institutes, small and medium enterprises, patients' associations and vaccine companies, with a joint interest to advance European cooperation in IVE studies, with a budget of 10 million euros funded equally by European Commission and the European Federation of Pharmaceutical Industries and Association. DRIVE's main goals were to establish a sufficiently sized network for robust, high-quality, brand-specific IVE estimates for all vaccines used in the EU in each season and to develop a sustainable and transparent governance model for public private partnerships.

Because it was the first-time vaccine performance for regulatory evaluation would be assessed through a PPP in Europe, DRIVE anticipated a long way of discussion to establish its study platform governance, ensure transparency, efficiency, and trust between partners and ultimately acceptability by authorities and peers, to achieve sustainability.

This document summarises the 5 years' work of DRIVE partners in developing the study platform governance, the methodology used and its final model and impact. It also discusses the challenges encountered, and more broadly the perspectives of public-private partnership-generated real-world evidence in vaccine effectiveness monitoring.

Introduction

The vaccine ecosystem is one of complexity, not just in terms of the product itself, but also in terms of disease surveillance, vaccines development and delivery, immunisation programs implementation and monitoring of vaccines performance. Everything within this ecosystem is interconnected and several key stakeholders interact in Europe (1, 2). Public Health Institutes (PHIs) are generally responsible for epidemiological surveillance and control of vaccine-preventable diseases, and for providing advice and guidance about the use of vaccines in national immunisation programmes. They establish disease surveillance systems and conduct studies to evaluate their vaccinations programmes implementation. To develop vaccines, companies conduct studies to understand the background epidemiology of the disease in the targeted population, then go through full clinical trial development to provide data requested for marketing authorisation. When their vaccines are approved, they have legal obligations to monitor the performance of these vaccines, by conducting real world studies on effectiveness and safety. The European Medicines Agency (EMA) is the organisation responsible for the vaccine's candidate evaluation for marketing authorisation. It is also the authority continuously monitoring the benefit/risk profiles of the vaccines in post-marketing setting and controlling that companies fulfil their obligations. In parallel, The European Centre for Disease Prevention and Control (ECDC) is coordinating PHI's activities to strengthen Europe's defences against infectious diseases and provide expertise, technical guidance, and funding to support disease surveillance and vaccines benefit risk monitoring.

In the vaccine post-marketing setting, the joint interest and mandate of public and private stakeholders to continuously monitor vaccination programs implementation and vaccines performance conducting Real-World-Evidence (RWE) studies point out the necessity to collaborate and communicate. Moreover, the EU diversity in terms of virus circulation, vaccinations programs, vaccine technology and vaccine uptake requires collective efforts to overcome the challenge of collecting large enough sample size for robust RWE and informed decision making.

In July 2016, the European Medicines Agency (EMA) published the 'guidelines on influenza vaccines' (3), in in which influenza vaccine effectiveness (IVE) studies requiring annual assessment by vaccine brand were included as one of the clinical requirements. Understanding the difficulties that vaccine companies face with this new regulatory obligation and the overlap with national PHIs' mandate to monitor their vaccination programmes, the EMA guidelines encouraged companies to liaise with organisations/institutions/public health authorities.

Since 2007/2008, EpiConcept coordinated the I-MOVE (Influenza Monitoring Vaccine Effectiveness in Europe) consortium, which included 23 partner institute sites from 18 countries. The I-MOVE consortium signed a framework contract with ECDC (ECDC/2014/026) related to measuring the effectiveness and impact of the influenza vaccines. Several discussions occurred between vaccine companies, the EMA and ECDC-I-MOVE, and it was proposed to combine efforts under an adjusted governance. The Innovative Medicines Initiative (IMI) was identified as a convenient pre-existing public-private

partnership (PPP) framework with a suitable legal and funding mechanism for joint action and governance boundaries in a post-authorisation setting, leveraging the ADVANCE guidance and lessons learnt. The Development of Robust and Innovative Effectiveness (DRIVE) project was set up in July 2017 to address the challenge of brand-specific IVE evaluation in the Europe (EU) through a PPP. The DRIVE project included, along 5 years, 16 partners from seven European countries, coming from PHIs (THL-Finland, ISS-Italy, FISABIO-Spain), universities (UNIFI-Italy, UCBL-France and University of Oxford-UK), research institutes (INSERM-France and OPBG-Italy), small and medium enterprises (P95-Belgium and Synapse-Spain), patients' associations and Foundation (CoMO-UK and IABS-EU France), and vaccine companies (Sanofi-France, GSK-Belgium, Seqirus-The Netherlands and Abbott-Netherlands) (Supplement 1), with a joint interest to advance European cooperation in IVE studies, with a budget of 10 million euros funded equally by European Commission (EC) and the European Federation of Pharmaceutical Industries and Association (EFPIA). DRIVE's main goals were to establish a sufficiently sized network for robust, high-quality, brand-specific IVE estimates for all vaccines used in the EU in each season and to develop a sustainable and transparent governance model for public private partnerships**.** Ultimately, the ECDC and I-MOVE network (Influenza Monitoring Vaccine Effectiveness in Europe) did not join or collaborate with the DRIVE IMI initiative, as, by principle, they preferred to remain completely independent to any collaboration with vaccine companies, especially given the sensitivity of the DRIVE project.

Because it was the first-time vaccine performance for regulatory evaluation would be assessed through a PPP in Europe, DRIVE anticipated a long way of discussion to establish its study platform governance, ensure transparency, efficiency, and trust between partners and ultimately acceptability by authorities and peers, to achieve sustainability.

This document summarises the 5 years' work of DRIVE partners in developing the study platform governance, the methodology used and its final model and impact. It also discusses the challenges encountered, and more broadly the perspectives of public-private partnership-generated RWE in vaccine effectiveness monitoring.

Methods

Because the **DRIVE study platform was a unique proof of concept**, several complementary methods were used to set up, develop and finetune its governance model over the 5 years project and ensure its acceptability, performance, and potential sustainability.

Governance guidance and principles

In 2017, the DRIVE project was built on the **four IMI cornerstones: joint interest** (PHIs monitoring their vaccinations programmes implementations; vaccine companies monitoring their vaccines Benefits/Risks (B/R) as part of their risk management plan required by EMA), **shared decision-making** process (project decision authority split equally between the public

consortium and the vaccine companies), **joint funding** (10 M€ project with 5 M€ from European Commission (EC) and 5 M€ from the European Federation of Pharmaceutical Industries and Associations (EFPIA)), **and transparent reporting** (IVE results submitted to EMA, IMI and available to the scientific community though the DRIVE website and in peer reviewed journals).

Under the IMI umbrella, the DRIVE study platform was set-up and developed using a specific governance model nested into the DRIVE project (Supplement 1). The DRIVE study platform governance fundamentals derived from the ADVANCE guidance and recommendations for post-authorisation vaccines monitoring (2): transparency, clear roles and responsibilities of partners, appropriately sized and efficient structure, mutual respect, and shared benefits. The DRIVE partners aimed to create a favourable environment for scientific exchanges and robust study conduct while ensuring appropriate management of potential conflicts of interest. In DRIVE, since the project was providing vaccine effectiveness estimates for regulatory obligations and vaccines company partners had a commercial interest, special attention was given to ensure IVE studies were not influenced by a potential conflict of interest.

Establishing a PPP to provide IVE estimates had the following advantages: a multi-stakeholders approach and scientific synergy to which each partner brings key added values (knowledge on implementation and effect of seasonal influenza vaccination programmes for PHIs and knowledge on related vaccines efficacy based on clinical trials for vaccine companies); synergy in resource allocation (access to influenza surveillance data and vaccine registers for PHIs and funding capacities for vaccine companies); and finally, synergy in communication (aligned and accurate communication about RWE IVE results). The anticipated disadvantages were the increased complexity and administrative burden due to the need to satisfy several stakeholders' mandates and obligations, especially the EMA's regulatory commitment for vaccine companies. Another disadvantage was the real or perceived potential conflict of interest for vaccine companies, emphasised by the fact that IVE studies used an observational design, which is considered by some as more susceptible to bias than randomised clinical trials.

Evaluation and monitoring framework

Because DRIVE was a unique brand-specific proof of concept, an evaluation and monitoring framework was developed to fine-tune the governance over the five years. It was based on principles previously established for assessing governance of health systems: strategic vision, participation and consensus orientation, rule of law, transparency, responsiveness, equity and inclusiveness, effectiveness and efficiency, accountability, intelligence and information and ethics (4). **The evaluation considered both the acceptability of the governance and its performance. The assessment was based on factual information extracted from reporting documents about IVE studies (dates, reports, budget) as well as experiences from DRIVE partners and views from external stakeholders, collected through surveys and workshops** (Supplement 2). The development of this framework and the DRIVE study platform evaluation were undertaken by a multi-stakeholder group within

the DRIVE project, with people coming from PHIs, a patient organisation, academia, and vaccine companies. Although the evaluations were not independently managed by a third party, a multi-stakeholder approach allowed to mitigate potential conflict of interest. The evaluations were performed after each influenza season between July and September. From them, the governance adaptations were proposed by this multi-stakeholder's group, then discussed with the DRIVE partners for final endorsement by the DRIVE decision-making body (the Steering Committee, with equal representation of DRIVE public and the vaccine company partners).

For the first season (2017-18), a single survey was conducted and used as a baseline to monitor the subsequent seasons using the complete framework. The evaluation and monitoring framework was finetuned in April 2019 and used for two consecutive full assessments of the 2018-19 and 2019-20 influenza seasons done respectively in July 2019 and September 2020. Because the governance was mature enough, partners' efforts for the two last seasons were focused on strengthening the stakeholders' engagement and developing an open data for research and secondary use framework (details below).

Stakeholders' engagement and communication strategy

To expand the DRIVE study platform and more specifically its network of sites able to conduct IVE studier, DRIVE partners developed a strategy based on three elements: 1) gather existing data leveraging national and regional surveillance systems involved in vaccine effectiveness monitoring activities conducted by PHI DRIVE partners, 2) optimise the IVE capacity by onboarding other PHIs willing to collaborate with DRIVE to enhance vaccine effectiveness monitoring in their region-country (notably Eastern Europe countries who were unrepresented), and 3) consolidate and continuously tailor an agile network through a yearly public call for sites/countries selection based on experience/expertise in IVE studies and on vaccine brand data needs.

Initial efforts to reach out to all potential sites was considered inefficient as it was not informed by vaccine availability, coverage, and capacity and thus in 2019 the strategy moved **to a more targeted approach by selecting the countries where influenza vaccine coverage reached a minimum of 30-40% for the elderly population.** Sites already collaborating with DRIVE in those countries were asked to increase their capacity when possible and new collaborators were sought. For the later, the dissemination of the public call for tender was **directly sent to clinicians and researchers who led respiratory viruses and influenza vaccines research groups**. In parallel, PHIs of the targeted countries were contacted, thanks to the DRIVE public partners and recommendations from the Independent Scientific Committee. **Finally in 2020, in agreement with regulators, DRIVE partners decided to focus on the most common recommended groups for vaccination with a relatively high vaccination coverage, as well as on settings with a high disease incidence**. Thus, for the subsequent 2020-21 and 2021-22 calls for tender, the scope was restricted to the population of 65 years and older and hospital setting.

EMA supported DRIVE from its inception. DRIVE was seen as a proof-of-concept project, leading to co-construction, with the informed recommendations from the EMA The liaison

with the EMA was coordinated by DRIVE public partner IABS-EU, from a multi-stakeholders group composed of representatives from vaccine companies (Sanofi, GSK, Seqirus and Abbott including their respective regulatory experts) and public consortium (FISABIO, THL and P95). Several discussions were engaged with EMA to align upfront on expectations for vaccine performance data and expected reporting from multi-Marketing Authorisation. A National Scientific Advice was organised in December 2020 to get recommendations and endorsement on the design and statistical analysis and the prioritisation of the IVE studies (target population and setting). This facilitated a dialogue to discuss shared challenges and hurdles in vaccine effectiveness monitoring implementation and results interpretation, including the expectations from authorities about VE robustness and what they consider informed results for decision-making.

The **DRIVE study platform communication strategy was focused on demonstrating the values of both public-private partnership and IVE estimation.** The first layer of the targeted audience was composed of regulators, governments, EU institutions and DRIVE stakeholders' peers. Key messages were finetuned along the 5 years and multiple channels, tools, and platforms were developed and used (Annual Forum meeting, webinars, workshops, conferences, journals, social media, press release, and newsletters). It was also acknowledged that governance is a complex topic to explain, especially when targeting scientists and researchers who are not necessarily familiar with formalised governance structures mainly used by large multinational organizations (such as the Global Fund, IMI or GAVI), and transparency is crucial to avoid, or at least minimise, suspicions of conflict of interest considering public and private interactions. Therefore, efforts were made to decrypt the DRIVE study platform governance. In 2019, **DRIVE produced a short video** (https://youtu.be/oitLQU2gyI8 - in English but additionally translated and subtitled into Spanish, Italian and French) **to explain how its governance operates, ensuring full transparency of the processes and presenting clearly shared roles and responsibilities between public and vaccine company partners**. Two other videos were produced to accompany the PPP governance messages: one video explaining DRIVE genesis and why a PPP was considered as a necessity (https://youtu.be/qXyCb5yYTEE) and another video presenting how DRIVE works in practice throughout an influenza season (https://youtu.be/chvBMtL-5gI). Those videos were designed by a communication agency (subcontracted third party) under the supervision of a multi-stakeholder's group, including communication experts' representatives, of several DRIVE partners coming from public institutes, a patient organisation, academia, and vaccine companies.

In 2021-22, DRIVE has intensified its cooperation with four patient groups to seek some insights on wider interest in knowing vaccine effectiveness rates and on lay public perception of PPP value. Those activities were driven by CoMO (DRIVE patient association), supported by a multi-stakeholders group of DRIVE partners (including communication experts) coming from public institutes, academia, and vaccine companies.

Open data for research framework

During the last two years of the project (2021 and 2022), DRIVE partners developed a **framework under which researchers, including external stakeholders (non-DRIVE partners), will be able to conduct additional secondary investigations and analyses using the DRIVE dataset**, even after completion of the DRIVE project in June 2022. DRIVE partners consider that this valuable database could be leveraged and further utilised for various purposes, such as Research and Development activities for a new generation of influenza vaccines, a contribution to the worldwide efforts to enhance a global surveillance network for respiratory viruses and associated diseases and monitoring of related vaccines' performance.

This open access to research data framework is aligned with European Commission–related guidance (5) and respects the legal obligations that were originally defined in the DRIVE IMI consortium agreement. Discussions were engaged to safeguard patients' rights and researchers' rights as well as ensure data quality and relevance of the research. Data standardisation, security, financial support, and communication were also addressed.

The development of this framework was undertaken by a DRIVE multi-stakeholder group, including legal and General Data Protection Regulation (GDPR) experts, with people coming from public institutes, a patient organisation, academia, and vaccine companies.

Results

Final governance model

Results of the evaluation and monitoring of the DRIVE study platform governance and consequently adaptations made to finetune its model are presented in Supplement 3.

The DRIVE study platform came to a model of collaborative framework with governance boundaries as detailed below.

The governance was articulated around **four main governance bodies**:

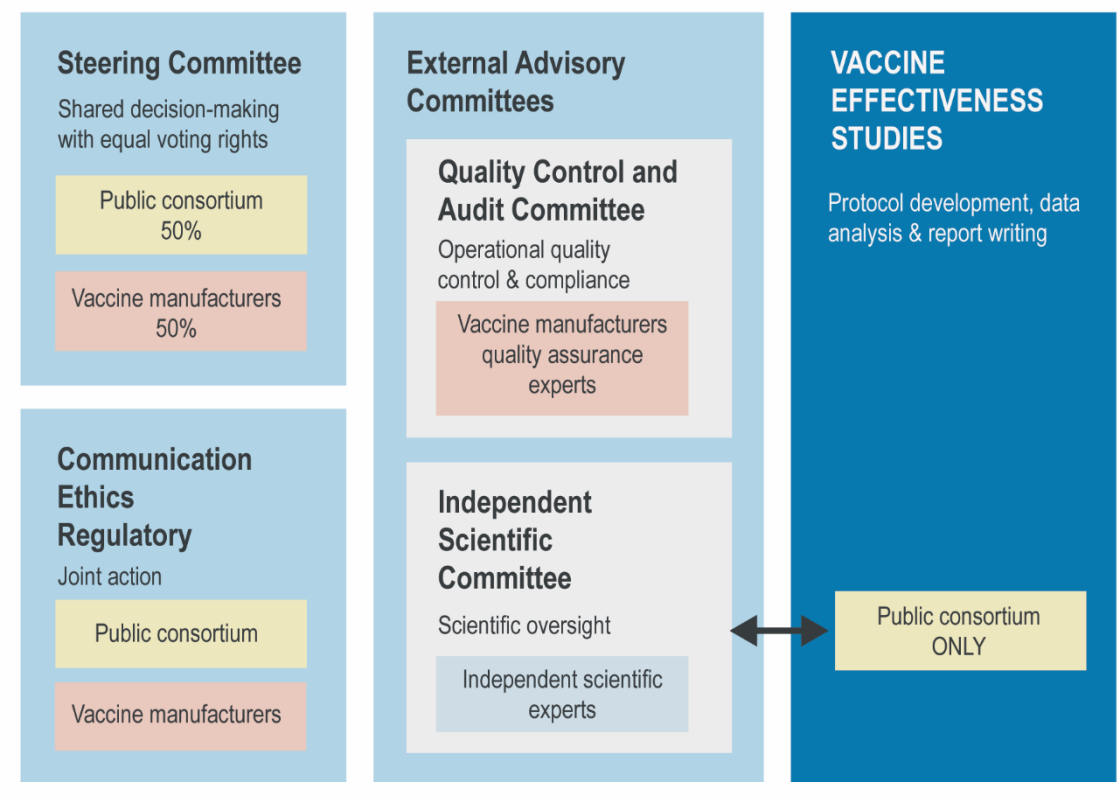

Figure 1: DRIVE study platform governance bodies

- The **Steering Committee (SC)** decided on the study platform's strategic direction, allocations of funds, and resources for the IVE studies. The steering committee was composed of representatives from the DRIVE partners who signed the consortium agreement. Decision authority was split equally between the public consortium (representatives from FISABIO [DRIVE public coordinator], THL, INSERM, OPBG, P95 and Synapse) and the vaccine companies (representatives from Sanofi [DRIVE EFPIA lead], GSK, Seqirus and Abbott).
- The **Study Work Package (WP7)** partners were responsible of the IVE studies conduct: development of the study documents (protocol, statistical analysis plan, seasonal report, and publication), data collection, pooled analysis, and results interpretations. The Study Working Package was composed of representatives of the public consortium (FISABIO, THL, P95, UNIFI, ISS, SURREY, UCBL, OPBG, INSERM). They worked closely with the Study sites.
- The **Independent Scientific Committee (ISC)** ensured the scientific oversight of the DRIVE study platform. Its mandate was to evaluate and endorse the IVE study documents (protocol, statistical analysis plan, seasonal report, and publications) and to provide advice on their review process and communication components. The ISC was composed on five experts in the areas of influenza vaccine effectiveness evaluation, statistics, influenza strain surveillance, vaccination programs, observational & database research, and clinical practice, having experience working in European and international academic institutions, public health organizations and regulatory agencies, and with no recent affiliation with any of the DRIVE partners. The ISC was composed of Hector Izurieta (US), Elisabeth Miller (UK), Mark Miller (US),

Stefania Salmaso (IT), and Marianne van der Sande (BE). ISC members signed an IMI advisory agreement with FISABIO (DRIVE public coordinator). They were engaged on a voluntary basis and were not paid for their contribution.

- The **Quality Control and Audit Committee (QCAC)** evaluated on a yearly basis the quality of the IVE study conduct, data reporting, and the pooled analysis from an operational, process and compliance perspective. They ensured good quality standards for observational studies in line with vaccine companies' EMA regulatory requirements. They provided recommendations to sites and the Study Work Package partners on the level of required quality management. The resulting quality reports were added to the IVE seasonal reports. The QCAC was composed of quality assurance experts from vaccine companies (representatives from Sanofi, GSK and Seqirus).

Ethics, communication, and regulatory activities were conducted jointly by DRIVE partners, thanks to several multi-stakeholders' groups of experts coming from public institutes, a patient organisation, a Foundation, academia, and vaccine companies.

The DRIVE Study platform governance operated around several processes:

- Public call and sites selection

  In February-March each year, a public call for tender was launched to select the sites (Research Collaborators) for the next influenza season. The call provided tender specifications in which eligibility and exclusion criteria, tender timelines, selection process and technical specifications were detailed. A template was provided to the site for application (Supplement 4 includes as an example, the Call for tenders 2021/2022 specifications and application form). The site was requested to complete the template providing information about previous work in the field of influenza and/or vaccines and technical-financial proposal for DRIVE.

  From April to June each year, the sites proposals were reviewed according to the following stepwise approach:

  - A **performance evaluation for sites who participated in the previous season**. It consisted in an assessment of the quality of the collected data, the respect of the data transfer timelines, and the overall relationship of the previous collaboration with the site as well as an assessment of the quality of the study conduct and related documentation. This qualitative assessment was performed respectively by two representatives of the Study Work Package (FISABIO the DRIVE public coordinator and P95 in charge of the data collection and pooled analysis) and the QCAC.
  - An **evaluation of the scientific relevance of the site application**. This qualitative assessment considered the adherence to the DRIVE generic protocols, the reliability of brand-specific information and laboratory testing, the ability to pool data (in terms of settings and age groups) as well as the expected sample size contribution proposed by the site based on previous seasons

(number of confirmed influenza cases at site level and vaccine coverage rate for targeted populations in the country/region). This assessment was made by the ISC.

- A **strategic review and budget allocation**. It consisted in evaluating the ability of the site to fill data gaps (targeted populations, settings, and brands), whether the site represented a new partner institution/country in the DRIVE studies, the feasibility of collecting COVID-19 data to account for pandemic impact and the ability to demonstrate cost-effectiveness/ co-founding and sustainability of the site application. This qualitative assessment was made by the Steering Committee.
- **Final sites selection was done by the SC with the advice of the ISC. The two committees** shared their assessments and built consensus towards a final decision. The allocated budget per site was appropriately sized to the related efforts (infrastructure and expected number of cases). The budget was split into a fixed and a variable part. The fixed part acknowledged the site staff's efforts to coordinate the study and pursue the expected surveillance period, whereas the variable cost accounted for the observed number of recruited subjects and performed testing, which varied by virus circulation.

In July, sites were contacted by FISABIO DRIVE public coordinator to proceed with the signature agreement and to organise a site visit/virtual meeting when needed. Ethical submissions were managed by site during summer/early September, to be prepared for the start of the influenza season expected around October/November at the earliest in some European countries.

- <u>Brainstorming sessions</u>

  Each year, brainstorming sessions were proposed to foster scientific exchange and leverage collaboration between scientific experts of the multi-stakeholder consortium. They were organised between the Study Work Package partners (public consortium partners) and the vaccine company partners to discuss IVE methods and upfront study document development (led by public partners). Along the project, these brainstorming sessions tackled several methodological and implementations topics, but also strategic questions related to the IVE studies. They included the following key questions: How to adapt ECDC IVE protocols for a best fit with EMA requirements; How to best pool the data for meaningful IVE results and what should be the threshold for relevant analysis; Should we use of a parsimonious approach for confounder adjustment; How to manage priority-setting of studies and platform expansion; How to account for COVID-19 pandemic on IVE studies, and How to value the DRIVE dataset thanks to secondary use of data. Those brainstorming sessions also allowed to discuss the DRIVE Study platform governance adaptations and processes improvement like the development of a mock report to define results presentation before obtaining data. Finally, the brainstorming sessions offered the opportunity to question the sustainability plan of the DRIVE study platform and to agree on how to move collectively in this changing EU vaccine ecosystem. The ISC members were consulted after those brainstorming sessions to get their advice.

- Study documents development and review process

  The study documents (core protocols, statistical analysis plan, seasonal report, and IVE publication) underwent a thorough and transparent review oversight by the ISC, which was coordinated by FISABIO (Supplement 5). The Study Work package partners (public consortium) wrote the study documents. The documents were circulated in parallel to the ISC and the vaccines company partners. (2) Vaccine company scientific experts provided consolidated written comments on the study documents. The ISC reviewed study documents and adjudicated on comments from vaccine company experts. The Study Work Package partners implemented the comments according to the ISC's recommendation and shaped the final version of the study documents.

- Data collection, analysis and reporting of IVE results

  Data collection was carried out at several independently operating study sites which was aligned with DRIVE core protocols. FISABIO as DRIVE public coordinator was the sponsor of the IVE studies. Sites remained owners of their data. Vaccine company partners were not permitted access to the individual site data or involvement in the conduct of the studies. A General Data Protection Regulation (GDPR) compliant IT infrastructure was established by P95 to centralise the data, perform the pooled analyses, and proceed with the results interpretations under the supervision of the Study Work package partners (Supplement 6). Secured and restricted access to the sites data, analysis environment and outputs were ensured by P95. The final version of the seasonal IVE results report was submitted by the DRIVE consortium to the EMA and IMI and published on the DRIVE website.

- Data quality control and quality management

  The IT infrastructure developed by P95, allowed to perform data quality control under their supervision.

  The QCAC performed yearly evaluation to assess the quality of the study conduct at site level and the quality of the processes in place at P95 for pooled analysis and results reporting.

  - Sites were asked to complete a "DRIVE Quality Management Questionnaire" (developed by a DRIVE multi-stakeholder' group). Based on sites feedback, the QCAC checked their processes and the quality of their documentation in compliance with DRIVE core protocols and local Standard Operating Procedures. The QCAC provided guidance and support to sites to improve the quality management system in place. Their recommendations included mainly ethical submission and protocol deviation documentation, personnel qualifications, training records, and data management specifications. Because the sites were not otherwise subject to the specific quality mechanisms applicable to vaccine company as per regulatory requirements, the QCAC was seeking for a reasonable and feasible mechanism to enhance the quality management of the DRIVE study platform.

- The QCAC evaluated the quality of the data management and pooled analysis for compliance with respectively the Data Management Plan and the Statistical Analysis Plan. They provided recommendations to P95 for improvements of the related documents.

The QCAC provided oversight of an audit conducted by a third party (external consultant auditor) in March 2022 on P95 activities related to the DRIVE study platform: data management, biostatistics and IT infrastructure for data transfer and storage. The proposal to conduct an audit was endorsed by the DRIVE steering committee (SC) in alignment with the auditee (P95). This independent assessment did not raise significant issues on the data integrity nor on the quality and the analysis of the IVE results. It served to enhance the P95 quality management systems and deliverables for DRIVE and for future relevant initiative(s).

- Submission of the seasonal IVE results reports and communication

  Seasonal IVE results reports (containing all the brands estimates) were submitted to the EMA jointly by the DRIVE consortium to fulfil the regulatory obligations of the vaccine companies involved. The EMA and the Vaccine Working Party (VWP) provided feedback on their assessment and conclusion. The seasonal IVE results reports were made publicly available on the website and discussed with the scientific community during annual forum meetings. DRIVE presented all calculable brand specific IVE estimates, regardless of precision or statistical significance. Public and private partners jointly developed seasonal lay summaries to present IVE results with educational and contextual information. In addition, IVE results were published in peer reviewed journals and presented at conferences.

- Open access for research data and secondary use

  DRIVE's test negative design database has grown along the five seasons of data (2017 - 2022) to include more than 35,000 patients, approximately 60 variables, and 13 vaccines. The established framework allows researchers, including external stakeholders (non-DRIVE partners), to conduct additional secondary investigations and analyses using the DRIVE dataset even after completion of the DRIVE project in June 2022

  This data framework is based on the following key guiding principles (Supplement 6):

  - Secondary use of data request shall be based on a scientific rationale, aiming to answer to a specific research question related to investigation on respiratory infectious diseases and their prevention.
  - Any entity (public or private) can apply to request for secondary use subject to meeting the criteria set upfront; the requestor could be either a DRIVE partner/site or an external stakeholder. However, pseudonymized subjects level data shall not be transferred out of EU/EEA. Only aggregated data which does not contain pseudonymized subject level data can be transferred out of EU/EEA for compliance with Article 44 of GDPR.
  - Collaborations with DRIVE partners and sites shall be encouraged for secondary use, especially with the aim to share data knowledge; any

detrimental impact on collaboration spirit promoted by the DRIVE Study platform shall be forbidden
- Secondary use shall not generate profit for any DRIVE partner.
- DRIVE studies were not designed for brands comparison and as such secondary use analyses shall not be foreseen for brands comparison; furthermore, access to competitors brands information shall not be allowed.
- Scientific publications must be foreseen for secondary use or at least disclosure of the outcomes in the public domain
- Secondary use of DRIVE data shall be subject to the approvals from the DRIVE sites and relevant governance bodies of the DRIVE study platform who assess the ethical, scientific relevance and feasibility of the request as detailed below:
    - FISABIO-P95 are the data custodian of the DRIVE dataset
    - The DRIVE ISC shall be responsible to assess the scientific & ethical relevance of the secondary use
    - FISABIO and P95 shall be responsible to assess the technical feasibility of the secondary use
    - The SC shall provide final approval for secondary use based (i) on the legal framework applicable to a given set of data (ii) on previous recommendations and potentially FTE/budget allocation considerations under DRIVE project remit
    - P95 shall be responsible to provide specific restricted access to data for secondary use purpose through the secure File Transfer Protocol (sFTP), in compliance with the GDPR standards
    - FISABIO-P95 shall ensure that any data made available is of sufficient quality to expect that the objectives of the secondary use of the data can be achieved and that subjects' privacy is protected in the processes of preparing and making data available for secondary use
    - Prior to data being released, FISABIO-P95 shall require the requestor to sign an agreement set to detail the conditions for secondary use.

Final governance impact

The established governance was a vehicle to bring the DRIVE study platform to its achievements as summarized below.
In 2021-22, the DRIVE Study platform concluded on:

- A **multi-stakeholders public-private partnership of 16 partners** from seven European countries, coming from PHIs (THL-Finland, ISS-Italy, FISABIO-Spain), universities (UNIFI-Italy, UCBL-France and University of Oxford-UK), research institutes (INSERM-France and OPBG-Italy), small and medium enterprises (P95-Belgium and Synapse-Spain), patients' associations and Foundation (CoMO-UK and IABS-EU France), and vaccine companies (Sanofi-France, GSK-Belgium, Seqirus-The Netherlands and Abbott-The Netherlands)
- a **large study platform,** included 13 sites covering 21 hospitals and more than 1,000 general practices in seven EU countries (Spain, Italy, France, UK,

Romania, Austria, Iceland) and one nationwide population-based cohort, in Finland
- a **unique and representative brand-specific vaccine effectiveness platform** capturing 67% of the Influenza vaccines available on the EU market (8 out of 12 vaccines)
- A **robust RWE platform** able to deliver some precise brand-specific IVE (with 95% CI < 40%) for informed decision-making (in 2019-20, for three brands of quadrivalent influenza vaccines)
- an **efficient RWE platform** able to deliver IVE results two months after the end of the influenza season (from end of April to early July)
- a cost-effective infrastructure spending an average of 800k€-1M€ per season for IVE studies integrating a variable budget to account for changes in influenza virus circulation (18% of budget save with COVID-19 pandemic)
- a fruitful scientific collaboration having produced five peer-reviewed scientific publications and 21 scientific communications in journals and conferences (as of end of June 2022)
- a **transparent and trusted public-private partnership** where partners as well as independent scientific members experienced valuable scientific interactions and no conflict of interest for vaccines evaluation
- a **framework for data sharing practices** and secondary analysis of the DRIVE dataset which already showed its interest (one request was already approved in 2021 and an analysis on confounders conducted and five new requests were received as of Mid-June 2022 and are under evaluation)

Discussion

Limitations

The success of the DRIVE study platform governance has been hindered by three main factors leading to a stalemate of the sites network expansion for the two last seasons (2020-21 and 2021-22) and limiting the robustness and meaningfulness of the produced brand-specific IVE results: **PHIs capacity and/or willingness to collect brand information, the impact of the COVID-19 pandemic in terms of influenza virus circulation and shift of interest/overload of staff, and finally PPP hesitancy and the ECDC's position towards DRIVE.**

In Europe, some PHIs with existing influenza surveillance system in place **did not collect brand information** and thus were questioning the value to collect this additional information knowing the effort it required (both in terms of GP/hospital staff and IT infrastructure update).

The lack of influenza circulation, partly due to the non-pharmaceutical interventions and lockdowns implemented to fight the **COVID-19 pandemic** (6), and the shift of attention and resources (both hospital and PHIs staff) to COVID-19 severely impacted the 2020-21 season and to a lesser extent the 2021-22 season (with a slightly observed higher influenza

circulation).

Some PHIs had strong **reluctance towards PPPs** and particularly the collaboration with vaccine companies. DRIVE made several attempts to engage in a discussion on methods, data-sharing practices, and governance principles collaboration, but perception of conflicts of interest remains an obstacle for them. Moving from methods and framework development (in ADVANCE project) to vaccine brand-specific evaluation in the post-authorisation setting (in DRIVE and COVIDRIVE), we observed a decreasing participation of PHIs in those projects, while their perception of conflict of interest increased. Their position had been reinforced by that of the ECDC towards DRIVE and the overlap and competition between DRIVE and other EU platforms/initiatives acting on behalf of the public sector to provide overall IVE (I-MOVE-ECDC).Without looking at the governance rules, the strongest detractors even argued de facto that "*the products of PPPs may result in pointless science and wasted effort*" (7). In response to the strong opposition, DRIVE's ISC published a reactive statement back in 2019, explaining that *"those arguments do not promote science and do not respect diversity. The views expressed on PPPs are prejudicial to the success of such endeavours since they may encourage a reaction by others to reject the findings as necessarily biased, without engaging in the detail of how such projects protect against conflicts and potential biases to ensure the independence and quality of their scientific outputs. In fact, it contributes to distorting general public perception and may even increase vaccine hesitancy by considering that the entities who develop and register the vaccines are not granted the ability to do good science*" (8).

Consequently, DRIVE public partners efforts made to invite PHIs to collaborate and share surveillance system data were limited to the on-boarding of only three new PHIs: Medical University of Vienna (MUV) - Austria (in 2017), Laboratoire National Santé (LNS)-Luxembourg (in 2019) and the Directorate of Health-Iceland (in 2020) who completed the three PHIs DRIVE partners (THL-Finland, ISS-Italy and FISABIO-Spain).

As a matter of fact, among the 14 targeted countries with influenza vaccine coverage rates around 40% and above for elderly population (by descending order: UK, Netherlands, Belgium, Spain, Portugal, Ireland, Italy, France, Sweden, Denmark, Finland, Luxemburg, Malta, Germany), a list of eight PHIs were identified in Q4 2019 for primary contact (PHE-UK, RIVM-Netherlands, Sciensano-Belgium, HPSC-Ireland, Santé public France-France, PHA-Sweden, SSI-Denmark and RKI-Germany). Six of them were contacted by DRIVE public partners before the COVID-19 pandemic was announced and one face to face meeting occurred with Sciensano in November 2019. Subsequent meetings and discussions occurred, unfortunately resulting in an unsuccessful ending (mixing and/or combining the three main factors listed above).

Perspectives

DRIVE provided a proof of concept for a viable approach for capturing brand specific vaccine effectiveness. The lessons learnt, infrastructure, study network and governance model built from DRIVE allowed to synergise in the area of COVID-19 pandemic to rapidly launch

COVIDRIVE, a project aiming to contribute to the monitoring of the COVID-19 vaccines performance in Europe. COVIDRIVE (https://covidrive.eu) is a PPP launched in June 2021, out of IMI umbrella, which currently brings together 11 partners: public institutions (FISABIO [Spain], THL [Finland]), an SME (P95 [Belgium]), and vaccine manufacturers (in order of joining the consortium: Sanofi [France], GSK [Belgium], AstraZeneca [UK], CureVac [Germany], Janssen [Belgium], Moderna [US], Valneva [France] and Novavax [US]). This partnership aims to conduct Master multi-country European studies to monitor COVID-19 vaccine effectiveness in real-world conditions. **The COVIDRIVE partnership was set up in nine months thanks to the existence of the DRIVE study platform and partner collaborations**, which has been extended to more partners and sites and adjusted to the COVID-19 pandemic, both in terms of scientific methodology and cost-sharing principles. The DRIVE fundamentals were used and adapted for COVIDRIVE development: the study platform (sites network, IT infrastructure, and study documentations), the collaborative framework and governance, the EMA consultations and regulatory submissions, and the transparency through the website (https://covidrive.eu/). **COVIDRIVE exemplifies the value of both existing RWE infrastructure and multi-stakeholder collaboration to repurpose a vaccine effectiveness platform under pandemic urgency. It was made possible thanks to the trust established between the DRIVE partners and the transparent and relevant governance model and mechanisms which convinced new vaccine companies to join.**

In 2021, while the scale-up and the sustainability of the DRIVE RWE infrastructure were discussed, the EU vaccine monitoring environment changed notably with the creation of a joint EMA/ECDC platform and the launch of a competing four-year VEBIS public-only platform (Vaccine Effectiveness, Burden and Impact Studies of Covid-19 and Influenza) supported by the ECDC (2021-2025) with a EUR 18 million invested for influenza and COVID-19 hospital networks. This raised the question of the need and value to have several initiatives in parallel, especially when competition for study sites is to be expected. Although the European Commission has embraced PPPs as an important avenue for future preparedness, underscored by the EUR 10 million overall invested in the DRIVE project (EUR 5 million coming directly from the EC and 5 million coming from EFPIA), there is a clear lack of coordination of stakeholders' roles and responsibilities and investments on vaccine effectiveness monitoring, which deserves to be tackled to ensure that EU citizens benefit from the joint public and private capacities for vaccines effectiveness monitoring and beyond.

Conclusion

The DRIVE study platform is an added value to the vaccine ecosystem, a multi-disciplinary platform that not only allowed scientific collaboration but also stimulated discussions around issues such as governance, the involvement of public health authorities, or the management of conflicts of interest. The final governance model of the DRIVE study platform showed how independence is not at odds with transparent collaboration with vaccine companies while IVE studies were conducted independently by public partners. The oversight of the IVE studies

by the ISC ensured the revision of methodologies and the mitigation of risks of potential conflict of interest by vaccine companies.

On 8 June 2022, as part of its final Annual Forum, DRIVE hosted a public roundtable bringing together key European stakeholders, including public institutions' representatives, to discuss the initiative's results after five prolific years. The panellist concluded that the DRIVE Study platform has been an interesting experiment in establishing a PPP model and an efficient network to conduct effectiveness studies. Taking stock of the lessons learned from the DRIVE Study platform will allow to understand whether this governance model can be used in specific circumstances or in any other case for which there is a need to generate additional evidence. It is necessary to study in detail the driving factors behind this public private hesitancy, which seem to have equivalent elements as vaccine hesitancy, and discuss in more detail how public partners can interact with vaccine companies, especially for authorities and stakeholders within the ecosystem that, unlike regulators, are not used to interacting with companies.

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Supplement 1 - DRIVE structure, governance and partners

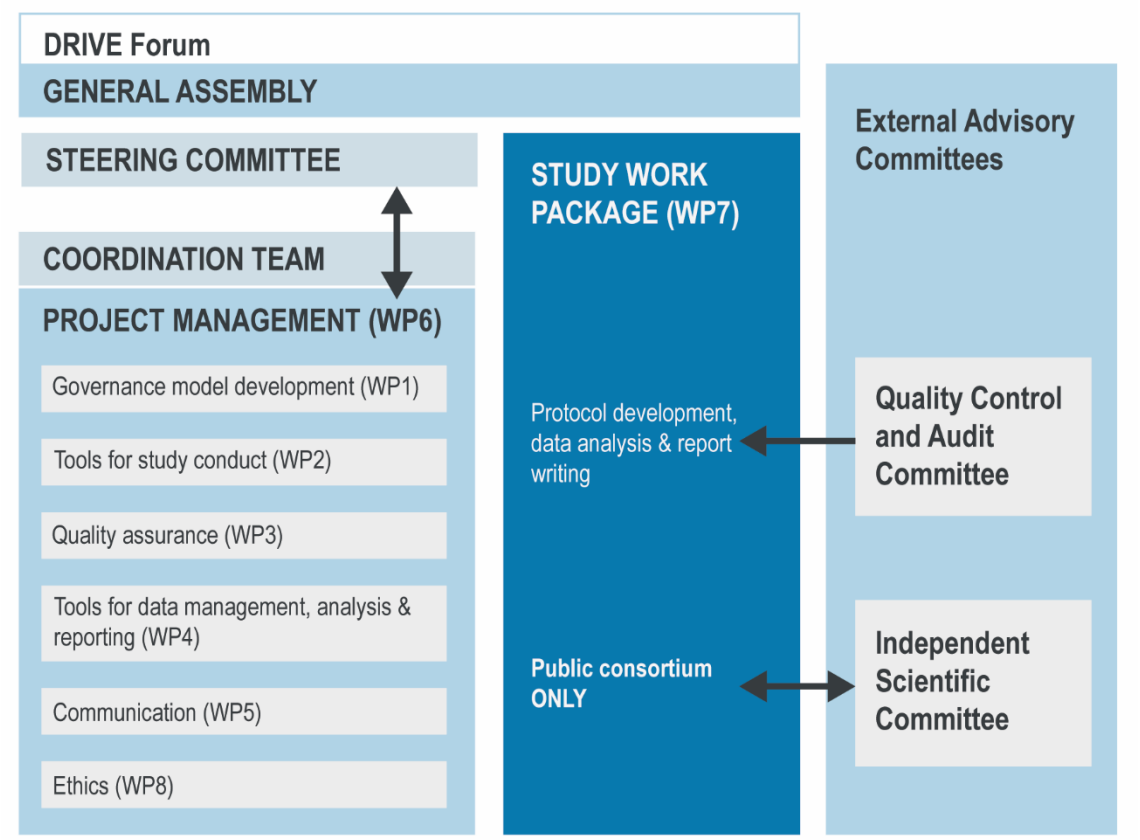


Figure S1. DRIVE operational bodies and work packages.

DRIVE is divided into several operational bodies (e.g., Steering Committee, Coordination team), work packages and independent bodies (the Quality Control and Audit Committee and the Independent Scientific Committee). As per IMI rules, the DRIVE project is structured into eight work packages (WP) focused on well-defined objectives: WP1: Development of a governance model for joint influenza vaccine effectiveness studies in Europe; WP2: Development of study tools; WP3: Evaluation of studies' quality and feasibility; WP4: Framework for analysis and study reports; WP5: Communication and dissemination of results; WP6: Project management, coordination and sustainability; WP7: Influenza Vaccine Effectiveness Studies; and WP8: Ethics requirements.
WPs tasks and deliverables are done as a joint public and private action except for the IVE studies (WP7), which are in the domain of public partners.

Consortium members

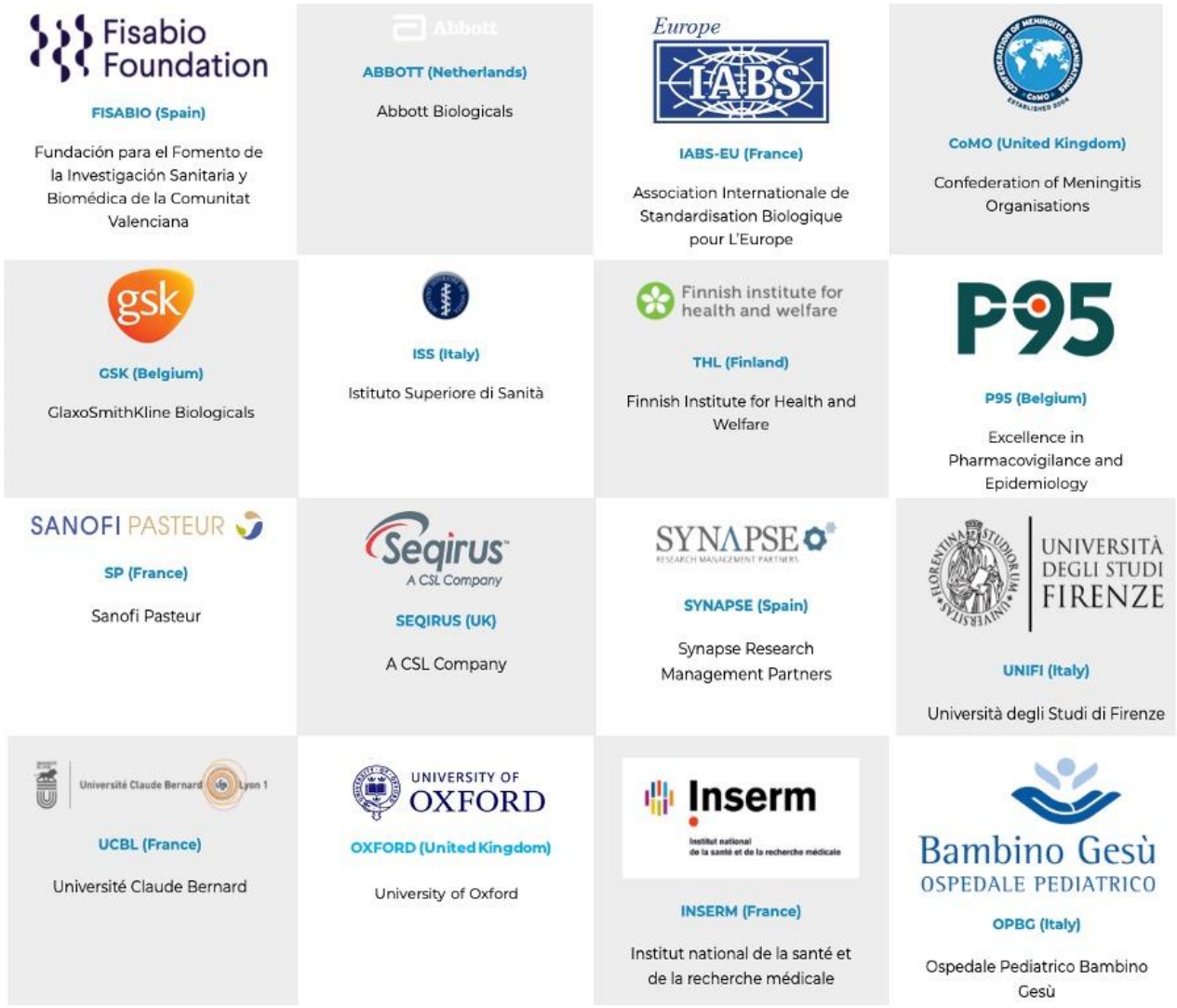


Figure S2. Consortium members

Supplement 2 – The evaluation and monitoring framework

Analytic framework

To evaluate the DRIVE study platform governance, 6 thematic areas were chosen as relevant for the governance evaluation [1] and further developed in 18 criteria for the DRIVE study platform governance evaluation (Figure S3). An analytic framework has been built around those criteria defining the questions of interest, the key performance indicators (KPIs) and their assessment methods (Table S1).

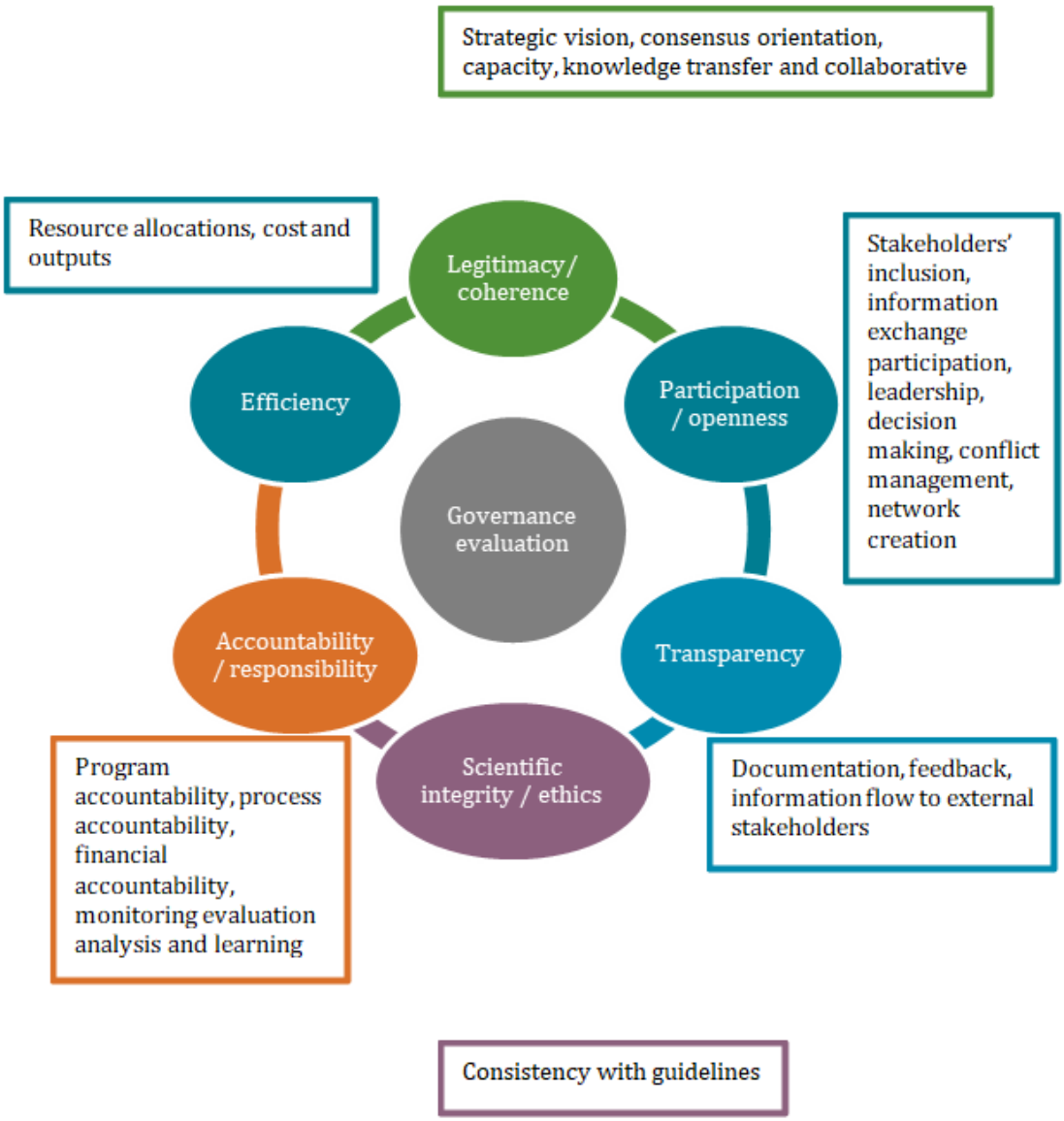


Figure S3: Study governance evaluation criteria

[1] *Sameen Siddiqi and all. Framework for assessing governance of the health system in developing countries: Gateway to good governance – Elsevier 2008 doi:10.1016/j.healthpol.2008.08.005*

Each area was disaggregated into criteria to capture as best as possible its full meaning and to express it in more operational terms (Table S1). From the criteria were derived broad questions. The broad questions were translated into specific questions and items that form the basic instrument for data collection. The methods for assessing the governance were categorized into reports and information collected through surveys/interviews/workshops. Key performance indicators were defined to get a measurable value of criteria. The framework asked altogether 47 broad questions across the 6 thematic areas and 18 criteria, ranging from contextual, descriptive, process related, and outcomes related. It included components assessing particular challenges public-private collaborations are facing in vaccine post-authorization setting (1): ensure common vision and joint interest of the multi-stakeholders approach, satisfy individual requirements coming from different partners, get scientifically robust and trusted outputs through a fully transparent study process (protocol, statistical analysis and report developments and reviews), ensure efficiency with an appropriate sizable structure. The method for assessing governance mixed factual information and perceptions. Factual information gathers operational components such as number of partners involved, number of studies and scientific deliverables, budget spent, delivery times and number of full-time equivalent staff; it was extracted from project management reports. Information on perception was gathered through surveys, workshops and interviews.

Table S1: Proposed analytical framework for monitoring and evaluating the performance of governance structures for public-private partnership

Thematic area	Criteria	Broad questions	Method(s)	Targets
Legitimacy/coherence	Strategic vision	• What are the objectives? • Is it valuable to have achieve sustainable • Is a PPC necessary to achieve the objectives?	Perception - partners and external stakeholder (Layer 1) surveys	• Ensure that PPC partners have a common vision • Collect external views about the legitimacy of the PPC • Annually assessed (at least initially)
	Consensus orientation	• Are key stakeholders fairly represented in the PPC? • How are decisions taken? • How are different stakeholder objectives reconciled? • Is the perception of the platform governance correct? (Using true/false questions)	Report and internal/external stakeholder surveys	• Ensure that platform is appropriately designed for PPC • Verify the transparency and clarity of the PPC governance and the roles of various bodies (committees)
	Capacity (competence and proficiency)	• Do the members of the PPC committees fulfil the needs, in terms of representativeness and expertise? • Should additional experts/competences be sought for inclusion?	Report and internal/external stakeholder and committee surveys	• Identify needs for additional or complementary expertise
	Knowledge transfer and collaborative learning	• What are the benefits for organizations participating in PPC? • What difficulties have been encountered? • What lessons have been learned from working with the public or private sector?	Perception – PPC partner survey	• Identify added value of collaboration
Participation/openness	Stakeholder inclusion	• Are any stakeholders missing from the PPC?	Perception – PPC external stakeholder surveys	• Identify potential needs for better representativeness
	Information exchange flow / participation	• What is the level of participation at meetings/conference calls/reviews • What is the delay for deliverables (document/minutes)? • How easily and quickly documents produced by the PPC are available to all members? • Is the frequency and structure of meetings satisfactory?	Report Perception – PPC partner survey	• Determine the level of exchange and critical pathway of communication within the PPC
	Leadership/ decision making / conflict management	• Are the decisions made by the governance bodies aligned with their mandates? • Are decisions made by committees effectively implemented? • Have any conflicts been well managed / resolved	Perception – PPC partner survey	• Evaluate the perception of joint public and private projects
	Network creation	• How were new associate partners integrated in the PPC? • Why did they accept to integrate into the PPC? • Had new associate partners been involved with professionally vaccine manufacturers? • Were the efforts to integrate new associate partners in the PPO appropriate and sufficient? • Are potential partners with technical expertise planning to integrate the PPP?	Report Perception – Independent committees, partner and external stakeholder surveys	• Determine the ‘attractiveness’ of the PPC

Thematic area	Criteria	Broad questions	Method(s)	Targets
		• What do the potential partners see as possible benefits / drawbacks?		
Transparency	Documentation	• Good traceability of the documents and related reviews within the PPC? • Do independent committee members have access to all relevant PPC information to perform their tasks?	Report Feedback from independent committees via surveys	• Evaluate the document review process
	Feedback (external à internal)	• What questions were frequently asked about the PPC governance? • Were clear and timely answers provided?	Report	• Determine the level of transparency through the interaction with potential new associate partners
	Information flow to external stakeholders	• What information is available on the PPC public website? • Are major decisions taken within the PPC appropriately communicated on the website? • How useful is the information on the PPC website for your organisation?	Report Perception - external stakeholder survey	• Determine the level of perceived transparency though the PPC public website
Scientific integrity / Ethics	Check consistency with relevant good practice guidelines	• Is the review process of scientific deliverables scientifically independent? • Does the PPC organisation and processes facilitate scientific integrity? • Is the PPC governance appropriate to provide robust and trusted scientific results?	Report Independent scientific committee feedback via survey Perception - external stakeholder survey	• Determine the level of scientific integrity
Accountability / responsibility	Program accountability	• Are deliverables from the PPC available on time	Report –	• Determine the level of accountability
	Process accountability (deliverables, SOP)	• Are internal guidelines followed? • How is the scientific review of deliverables organised within the PPC? • What is the added value of the QCAC?	Report Report – Independent Scientific Committee feedback via survey Report- QCAC feedback from survey	
	Financial accountability	• Is the budget allocated for data generation appropriately sized? • Is the budget allocated for data generation appropriately used??	Report	
	Monitoring evaluation and learning	• Are evaluation results well implemented?	Report àstarting 2nd year based on baseline evaluation and resultant action plan	
Efficiency focus on outcomes	Resource allocation	• Is the time spent by the partners for the project adequate to achieve the tasks and to produce the scientific deliverables? • Is it appropriate and sustainable that committee members are reimbursed for travel but not paid for time? • What would be required for sustainability?	Report + feedback from independent committees via surveys Perception – PPC external partner surveys and feedback from independent committees via surveys	• Determine the level of efficiency
	Cost and outputs	• Is the project cost-effective based on benchmark?	Report	

Supplement 3 – Results of the evaluation and monitoring of the DRIVE study platform governance: governance adaptations

Table S2: Principal results from monitoring and evaluation of the DRIVE governance structure

Criteria	KPI	season 2017-18 (n/number of responders)		season 2018-19 (n/number of responders)		season 2019-20 (n/number of responders)	
		DRIVE Partners	External stakeholders	DRIVE Partners	External stakeholders	DRIVE Partners	External stakeholders
Strategic vision	Importance of brand-specific IVE	14/15	10/10	26/27	16/16	21/24	11/11
	Appropriateness of PPC	15/15	7/10	26/27	11/14	23/24	10/11
Consensus orientation	Role of ISC	13/15	8/9	24/26	14/15	21/22	11/11
	Role of QCAC	10/14	5/9	19/26	11/13	15/22	7/11
	Site selection	9/11	5/9	13/22	NA	12/12	10/11
Scientific integrity / ethics	Platform perceived as being robust and trustworthy	13/15	5/9	18/26	12/13	20/24	10/11
Network creation	Efforts to integrate new research collaborators	6/11	NA	21/26	NA	NA	NA
Process	Organisation of review process for study platform deliverables	8/11	NA	15/22	NA	10/12	9/11

Results were extracted from surveys and workshops
Some questions were skipped by responders

Each question had five levels of responses – these data here correspond to the two highest, e.g., very appropriate and quite appropriate
NA: questions were not asked

Table S3: Summary of the main modifications made on the DRIVE study platform governance

Study platform governance			
2017-18 influenza season	**2018-19 influenza season**	**2019-20 influenza season**	**2020-21 and 2021/22 influenza seasons**
New collaborators were selected by the Steering Committee (SC) on a yearly basis through a public call with pre-defined criteria	New research collaborators/sites were invited to join DRIVE on a yearly basis through a public call. Their selection was organised in a 2-step approach: the Independent Scientific Committee (ISC) performed the scientific evaluation of the new research collaborators/sites proposals and provided its recommendations to the SC who then performed the strategic selection and decided the allocated budget. DRIVE developed a chart and core open data model to promote open access strategy and increase its study platform.	Call for tenders, the sites selection was organised in a stepwise approach coordinated by SYNAPSE and FISABIO. In step 1 the ISC performed a scientific evaluation of the sites proposals consisting of a quantitative evaluation, scoring and ranking of the proposals was based on five pre-defined criteria. After the ISC members made their evaluation, FISABIO organized an ISC meeting in which the ISC members presented their evaluations and the whole ISC committee agreed on the final scientific evaluation and on general recommendations. Then, the ISC members provided to FISABIO/SYNAPSE the scientific evaluation with the list of questions / clarifications to be addressed to the sites and to be sent to the SC for the strategic selection of the sites and allocation of the budget in step 2.	Call for tenders, the site selection process was adjusted, and an extra step was added (3 steps approach), coordinated by FISABIO and SYNAPSE. Changes implemented included: o Predefine the scope in the call for tender specifications (inclusion & exclusion criteria). o Get feedback on sites that have collaborated the previous season(s). o Simplify ISC evaluation criteria. o Increase the value of data poolability and sample size contribution. o Refine ISC role for final selection of sites. In step 1, the QCAC and P95 evaluated the performance of sites previously involved with DRIVE, based on the quality of the data collected in previous seasons and quality of the study conduct. In step 2, the ISC performed a scientific evaluation of the sites proposals consisting of a qualitative evaluation of the proposals based on 2 pre-defined criteria (scientific relevance for DRIVE and Evaluation of the estimated sample size / vaccine coverage for VE). After the ISC members made their evaluation, FISABIO organized an ISC meeting on which the ISC members presented their evaluations and the whole ISC committee agreed on the final scientific evaluation and on general recommendations. Then, FISABIO/SYNAPSE circulated the scientific evaluation to the SC and the list of questions/clarifications to be addressed to the sites. SC performed the strategic selection of the sites and allocation of the budget based on P95/QCAC and ISC evaluation. Finally, in step 3, DRIVE SC and ISC met to share assessments and build consensus for final sites selection, including conditional approval of the proposals.

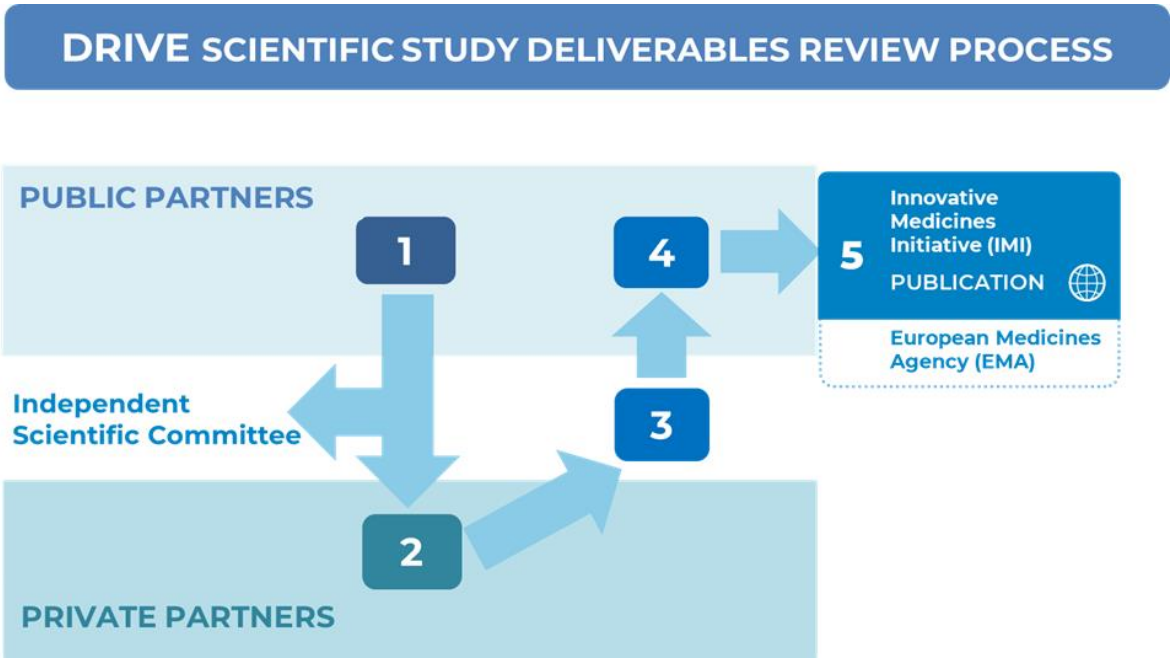
Study platform governance			
2017-18 influenza season	**2018-19 influenza season**	**2019-20 influenza season**	**2020-21 and 2021/22 influenza seasons**
Study documents (protocols, statistical analyses, reports and publications) were assessed by the ISC. Vaccine company experts provided written comments on these documents to the ISC. They did not have access to the data and were not involved in the conduct of the studies	No change except the process was streamlined. The study documents were reviewed initially by the ISC, followed by integration of their comments in the deliverable. The documents were then sent to the vaccine company experts who provided consolidated comments to the ISC, who reviewed them and sent them to the document owners for finalisation before submission to IMI	A mock report was developed to define results presentation before obtaining data	The process was streamlined in each subsequent season (parallel reviews made by ISC and vaccine company experts), and timelines shorten while study documents had been improved from previous seasons.
The QCAC advised on compliance and quality of the studies	The QCAC assessed the quality of the study conduct, the data collection and the pooled analysis. The quality report with their conclusions was attached to pooled analysis report, which was reviewed by the ISC review before submission to the EMA. The QCAC described how the quality of the data was assessed for the current influenza season and provided recommendations for improvement for the following season.	Because the sites were otherwise not subject to the specific quality mechanisms applicable to vaccine company as per regulatory requirements, the QCAC was thus seeking for reasonable and feasible mechanism to enhance the quality management. They provided guidance and supported sites to get the relevant study documentation and quality management system in place. Quality management questionnaire was updated and sites feedback analysed.	The season was marked by the near-absence of influenza circulation in Europe. Consequently, QCAC routine activities with sites were of limited value to conduct for the 2020/2021 season and the focus was for the preparation of the independent evaluation of P95 that took place in season 2021/22.

Supplement 4 – Public call for tenders

Call for tenders 2021/22 Specifications

Call for tenders 2021/22 Application form (for study sites)

Supplement 5 – Study documents development and review process



Supplement 6 – Open access for research data Framework

Executive Summary

While RWE is playing an increasing role in healthcare decisions (1) and the COVID-19 pandemic may have accelerated open data and access practices (2, 3), those practices deserve to be carefully managed to safeguard patients' rights and researchers' rights and ensure data quality and appropriate results interpretation for informed decision-making (4). Existing data-sharing systems and frameworks are facing many big challenges and problems (5) such as, but not limited to, data standardisation, security, financial support, and communication.

DRIVE's test negative design (TND) database has grown along the five seasons of data (2017 – 2022) to include more than 35,000 severe acute respiratory infection (SARI) patients, approximately 60 variables, and 13 vaccines. DRIVE partners consider that this valuable database could be leveraged and further utilised for various purposes, such as Research and Development activities for a new generation of influenza vaccines, a contribution to the worldwide efforts to enhance a global surveillance network for respiratory viruses and

associated diseases and monitoring of related vaccines' performance. Therefore, DRIVE has established a framework under which researchers, including external stakeholders (non-DRIVE partners), will be able to conduct additional secondary investigations and analyses using the DRIVE dataset, even after completion of the DRIVE project in June 2022. This open access to research data framework is aligned with the European Commission–related guidance (6) and respects the legal obligations that were originally defined in the DRIVE IMI consortium agreement.

Definitions

- "**Open access**" is defined as the practice of:
  (i) providing on-line access to scientific information that is free of charge to the reader (e.g., free online access to scientific peer reviewed papers);
  or
  (ii) allowing data sharing and reuse for research purpose(7).

- "**Primary use of data**" means the use of subject personal data health information for analysis, research, quality/safety measurement, public health and marketing or other activities which were defined upfront as the primary intent for the collection of data.

- "**Secondary use of data**" is defined as the use of subject personal data health information for another purpose or intent than the one defined for the data collection.

- "**Open access for research data**" refers to the terminology used in Horizon 2020 guidance (6)**.**

Scope

The established framework allows researchers, including external stakeholders (non-DRIVE partners), to conduct additional secondary investigations and analyses using the DRIVE dataset even after completion of the DRIVE project in June 2022.

The DRIVE dataset includes (see Annex 1 for more details on DRIVE data definitions):

- pseudonymized subject level data collected from surveillance systems established by national or regional public health institutes and shared with DRIVE for IVE pooled analysis
- pseudonymized subject level data collected from research institutes/public organizations (hospitals, GP networks) who conduct a study and collect data specifically for DRIVE IVE pooled analysis.

Secondary investigations and analyses request shall be based on a scientific rational aiming to answer to a specific research question

Pre-established settings

DRIVE study platform and dataset

Data collection was carried out at several independently operating study sites which constituted the DRIVE study network. This network was composed of both national/regional public health institutes who shared data collected through their surveillance systems and research institutes/public organisations (hospitals, GP networks) who conducted a study and collected data specifically for DRIVE purpose answering to a call.

Sites collected epidemiological data (clinical data, virus testing and vaccination information) from patients presenting with Influenza like illness symptoms (ILI) or Severe Acute Respiratory Infection (SARI) who visited their general practitioner or hospital during the influenza seasons (from October to April each year) in several European countries. The data was collected and shared for a purpose defined beforehand in the DRIVE core study protocols.

Data coming from all sites was centralized in a central data platform which is General Data Protection Regulation (GDPR) compliant, and which uses a modular compartmentalized design for data sharing, with a controlled and secure user management (Annex 2).

Collected data was provided with a number identifying information related to the site and patient which qualified them as personal data pursuant to Article 4 of GDPR.

Details about data terminology and variables are summarized on the Annex 1. Short description of the Central IT platform is available in Annex 2.

DRIVE Legal environment, data privacy and intellectual property

The DRIVE study platform was nested into the DRIVE project under a specific IMI consortium agreement (CA) which was concluded between the DRIVE partners and corresponded to a 5-year engagement (July 2017-2022). As per the CA and related study platform governance, the following boundaries should be considered for the open access for research data framework:

- FISABIO, as DRIVE coordinator, was the sponsor of the IVE studies and had a specific agreement with each study site (called Research collaborators or Associate partners) for data collection/data sharing. Some DRIVE partners (FISABIO, THL, ISS and Oxford university RCGP-RSC) were sharing data as per their commitment in the DRIVE consortium agreement.
- Study sites remain the owners of their respective pseudonymized subjects level data (refer to Annex 2) and provided an automatic cost-free perpetual license to FISABIO for IVE pooled analysis and for subsequent secondary use of data.
- Along the DRIVE project, the **central data platform (ESSA)** for data collection, pooled analysis and dataset storage was hosted by P95, a DRIVE partner. Data was stored in Belgium, on a server hosted by Uniweb BVBA, with its datacentre with InterXion in Zaventem, Belgium (Annex 2)[1].

[1] After June 2022, the DRIVE dataset will be maintained by P95. Secure File Transfer Protocol (sFTP) will be used to download data from the central data platform

- Vaccine company partners were not permitted access to the data or involvement in the conduct of the IVE studies.
- FISABIO was the owner of the DRIVE Study Results (anonymised aggregated analytical dataset and study report including tables and figures – refer to Annex 2) and provided license for research to DRIVE partners
- Each site was responsible for the collection and pseudonymisation of the subject data in accordance with their applicable data protection law and ethical obligations.
- The secondary use of data coming from 2017-2021 influenza seasons was not covered by the informed consent until the season 2021/22. Hence, to the extent that the provision of such information individually is nearly impossible or would require disproportionate efforts, a collective information shall be implemented at a DRIVE website to be able to use again these data for new purposes (secondary use). This information notice shall be designed in accordance with article 13 & 14 of the GDPR. The latter shall inform data subjects of the secondary use of data, its purposes & shall serve as a reminder of the pseudonymisation process.
- For new season 2021-22, a specific wording was added in the Informed Consent Form to identify, inform & collect data subjects' consent about the secondary use of data.

Guiding principles

1. Scope and relevance	
1.1	Secondary use of data request shall be based on a scientific rationale aiming to answer to a specific research question.
1.2	Secondary use purposes shall be related to investigation on respiratory infectious diseases and their prevention
1.3	Collaborations with DRIVE partners and sites shall be encouraged for secondary use especially with the aim to share data knowledge; any detrimental impact on collaboration spirit promoted by DRIVE shall be forbidden
1.4	Secondary use shall not generate profit for any DRIVE partner. Agreement to set the secondary use conditions shall be handled by Fisabio-P95 with predefined fees covering contract and data management foreseen workload.
1.5	DRIVE studies were not designed for brands comparison and as such secondary use analyses shall not be foreseen for brands comparison due notably to the followings: DRIVE project was not launched to perform head-to-head comparisons

	between vaccines, referred to as relative vaccine effectiveness, nor it was designed to permit direct comparison between vaccine performances - When IVE was estimated in DRIVE, a comparison was made between vaccinated groups and non-vaccinated groups. This was also referred to as “absolute VE” and served the purpose of understanding the protective effect of a vaccine. This provided information which could be used to assess the benefit/risk balance of a vaccine in line with the guidance from the European Medicines Agency. - There were major challenges which prevented comparison of vaccine effectiveness between different vaccines brands. For example, the comparability of the two groups receiving the two different vaccines would need to be ensured. Multiple factors determine VE, and these operated even when several vaccines were used in the same setting and were exposed to the same circulating virus strains (e.g., due to specific recommendations or to healthcare professional practices, even in the same setting, different vaccine brands were given to different subgroups.
1.6	Secondary use framework shall not be used by a vaccine company to get access to competitor brands information even through a third-party application/request
1.7	Scientific publications must be foreseen for secondary use or at least disclosure of the outcomes in the public domain
2. Governance	
2.1	Secondary use of DRIVE data shall be subject to the approvals from the DRIVE sites and relevant governance bodies who shall assess the ethical, scientific relevance and feasibility of the request.
2.2	FISABIO-P95 are the data custodian of the DRIVE dataset
2.3	FISABIO as DRIVE coordinator shall implement the framework and ensure good coordination between DRIVE governance bodies, partners, sites
2.4	The DRIVE Steering Committee shall oversee development and operation of all secondary use
2.5	The DRIVE Independent Scientific Committee shall be responsible to assess the scientific & ethical relevance of the secondary use
2.6	FISABIO and P95 shall be responsible to assess the technical feasibility of the secondary use

2.7	The Steering Committee shall provide final approval for secondary use based (i) on the legal framework applicable to a given set of data (ii) on the previous recommendations on 2.5 and 2.6.
2.8	P95 shall be responsible to provide specific restricted access to data for secondary use purpose
2.9	FISABIO-P95 shall ensure that subjects' privacy is protected in the processes of preparing and making data available for secondary use
2.10	FISABIO shall ensure that information about approved secondary use of data requests are disclosed on DRIVE website in full transparency.
3/ Sites-subjects control of data	
3.1	Site can opt out of having their local data used for secondary purposes (pseudonymised subjects level data) *Note: by signing the Informed Consent Form, participants agreed both to take part in the study and that their personal and coded data may be used for secondary purposes.*
4/ Requesting and accessing data for secondary use	
4.1	The DRIVE Steering Committee shall assess applications based on the rationale for secondary use of data
4.2	Any entity (public or private) can apply to request for secondary use subject to meeting the criteria set upfront; the requestor could be either a DRIVE partner/site or an external stakeholder; However, pseudonymized subjects level data shall not be transferred out of EU/EEA. Only aggregated data which does not contain pseudonymized subject level data can be transferred out of EU/EEA for compliance with Article 44 of GDPR.
4.4	When a requestor seeks access to data as a third party for another entity, the requestor shall not generate profit solely from getting access to data
4.5	FISABIO-P95 shall ensure that any data made available is of sufficient quality to expect that the objectives of the secondary use of the data can be achieved
4.6	Access to aggregated data shall be primarily proposed when adequate for secondary use analysis.
4.7	Prior to data being released, FISABIO shall require the requestor to sign the agreement set to detail the conditions for secondary use

4.8	Once the request is approved, P95 shall provide specific restricted access to data for secondary use purpose through the secure File Transfer Protocol (sFTP), in compliance with the GDPR standards

Process

Several processes are needed to consider, determine, monitor, and report on a request to use DRIVE data for secondary purposes. Processes and the roles and responsibilities of the parties involved are presented in a stepwise approach in the **Figure 1** below.

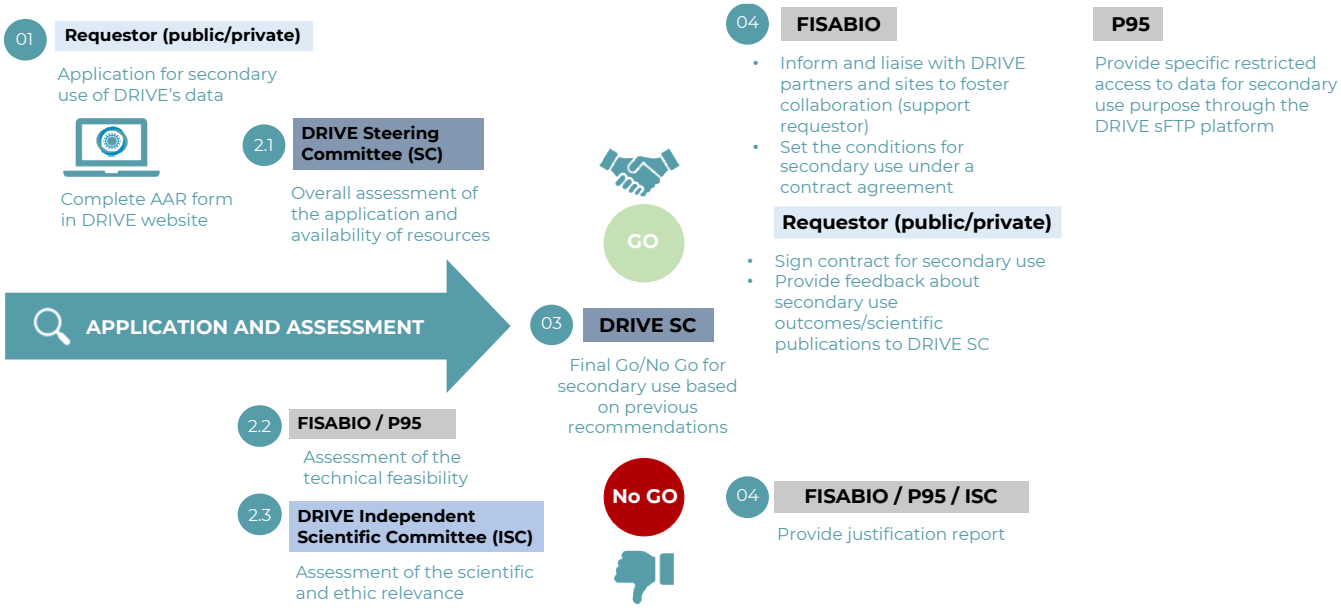


Figure 1: Process for assessing DRIVE use of secondary data.

Step	Description of process	Responsibility
1	Submit an application for secondary use by completing the Additional Analysis Request (AAR) form available in DRIVE website.	The requestor/applicant
2	Coordination of the application assessment and approval	FISABIO
2.1	Assess application in terms of intended use & required Privacy Authorizations (Data Privacy Authorities Authorization for the Requestor, Data Protection Impact Assessment, Reference Methodology if any). Scientific relevance is also in the scope of the Steering Committee assessment.	The Steering Committee
2.2	Assess the technical feasibility of the secondary use	FISABIO and P95

2.3	Assess the scientific & ethical relevance of the secondary use	DRIVE independent Scientific Committee
3	Provide final approval for secondary use based on previous assessments	The Steering Committee
4.1	Inform and liaise with DRIVE partners and Sites to foster collaboration	FISABIO (support Requestor)
4.2	Set the conditions for secondary use under a contract agreement	FISABIO
4.3	Sign the conditions for secondary use	The requestor/applicant and FISABIO/P95
4.4	Ensure proper information and transparency of secondary use project on DRIVE website	FISABIO
4.5	Provide specific restricted access to data for secondary use purpose through the secure File Transfer Protocol (sFTP)	P95
4.6	Provide feedback about secondary use outcomes /scientific publication to DRIVE steering committee	The requestor/applicant

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Annex 1: Data terminology

The following categories of data are considered to establish the secondary use framework:

For a given influenza season – under DRIVE core protocols (objective: Brand specific Influenza vaccine Effectiveness)

- **Level 1:** Raw site subject level data: data remaining at Study site level. Pseudonymisation of the raw subject level data is done at the Study site level.
- **Level 2:** Cleaned pseudonymised site subject level data (called "Site Dataset"): data at study site level which corresponds to all subject's data. A copy is transferred to P95
- **Level 3a:** Cleaned pseudonymised subject level data across sites (called "DRIVE Database"): data coming from all study sites centralised at P95 level. The DRIVE Database is based on the Level 2 data from all study sites to P95 under the study agreement(s) with FISABIO and contains all subject's pseudonymised data of a given season. The DRIVE database contains data of multiple vaccine brands as per the study design used.
- **Level 3b:** Pseudonymised subject level analytical dataset: This dataset is used for the seasonal analysis at P95 central level (pooled across sites). This analytical dataset contains the vaccine brands of interest.
- **Level 4:** Anonymised aggregated analytical dataset(s): This aggregated dataset is specific to a given season and contains only the vaccine brand(s) of interest
- **Level 5:** Tables/figures and listings presenting the study(ies) outputs: annex of the Study Report(s).

All personal data (Level 1 Data, Level 2 Data and Level 3 Data) is subject to GDPR data protection considerations as defined in the core Protocol and related Informed Consent Form.

Annex 2: IT infrastructure for data collection, pooled analysis and secondary use

DRIVE developed a central data platform for data collection and analysis, hosted by P95 DRIVE partner, which is General Data Protection Regulation (GDPR) compliant, uses a modular compartmentalized design for easy scale up and data sharing, with a controlled and secure user management, and integrated data quality processes.

DRIVE data flow was the following (Figure 2), corresponding to the data levels defined in Annex 1:

- Sites prepared data following DRIVE Minimum dataset requirements (defined in the core study protocols)
- Secure data upload was done by site through the DRIVE Electronic Study Support Application (ESSA), a web-application with controlled access through user authentication; it included multiples functionalities like automated data quality control, data visualization and a monitoring tool[2]

[2] After June 2022, the DRIVE dataset will be maintained by P95. Secure File Transfer Protocol (sFTP) will be used to download data from the central data platform

- Data was stored in the ESSA environment, and data privacy was checked
- Data was analysed in a Central analysis environment which ensured controlled access to statisticians
- Tabular and graphical summaries were moved to Output environment

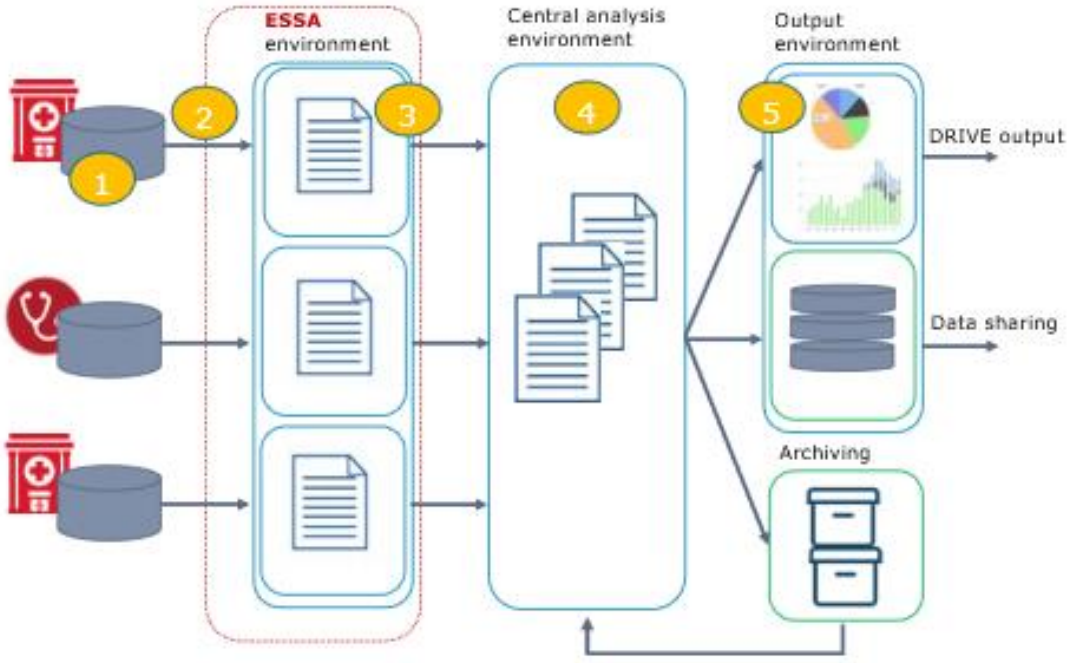

Figure 2: DRIVE data flow