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Development of Robust and Innovative Vaccine Effectiveness

WP1 – Governance

D1.4 Real-World Evidence infrastructure for vaccine effectiveness monitoring in Europe: from proof of concept to sustainability

DRIVE IMI project white paper

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Abbreviations

ADVANCE - Accelerated Development of Vaccine benefit-risk Collaboration in Europe
B/R - Benefits/Risks
CVE - COVID-19 vaccine effectiveness
DRIVE - Development of Robust and Innovative Vaccine Effectiveness
EC - European Commission
ECDC - European Centre for Disease Prevention and Control
EFPIA - European Federation of Pharmaceutical Industries and Associations
EMA - European Medicines Agency
GDPR - General Data Protection Regulation
I-MOVE - Influenza Monitoring Vaccine Effectiveness in Europe
IMI - Innovative Medicines Initiative
ISC - Independent Scientific Committee
IVE - influenza vaccine effectiveness
MAH - Marketing Authorisation Holder
PHI - public health institute
PPP - public-private partnership
py - person-years
QCAC - Quality Control and Audit Committee
RWE - Real-World Evidence
SARI - severe acute respiratory infection
SME - small-medium enterprise
TND - test-negative design
VEBIS - Vaccine Effectiveness, Burden and Impact Studies of Covid-19 and Influenza
VWP - Vaccine Working Party

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Abstract

To complement clinical trial evidence of antiviral vaccines with real-world data, platforms for surveillance, virus circulation and vaccine safety and effectiveness are needed. Because of the complexity, this may best be done by combining efforts between public and private sectors, developing a multi-stakeholder approach. Public-Private-Partnerships increasingly play a critical role in combating infectious diseases but are still looked at with some reservations.

The Development of Robust and Innovative Vaccine Effectiveness (DRIVE) project established a platform for measuring brand-specific influenza vaccine effectiveness in Europe upon a request for the European Medicines Agency (EMA). To this end, a multi-stakeholder public-private partnership of 16 partners from seven European countries was set up, coming from public health institutes, universities, research institutes, small and medium enterprise, a patient association, a foundation, and vaccine companies. The consortium managed to create a unique large robust and efficient study platform, which included 13 sites covering 21 hospitals and more than 1,000 general practices in seven EU countries. Using this platform 67% of the influenza vaccines on the EU market could be captured, delivering brand-specific IVE within two months after the end of the influenza season. A transparent public-private collaborative framework with governance boundaries was the vehicle to bring the DRIVE initiative to these achievements. Scientific collaborations were foreseen while independent scientific oversight ensured the mitigation of risks of potential conflict of interest by vaccine companies.

As a spin-off, the DRIVE platform could rapidly be repurposed as a COVID-19 vaccine effectiveness platform under pandemic urgency; COVIDRIVE was set up in 9 months.
DRIVE partners hope that considerations will be given to the DRIVE public private collaborative model in the ongoing dialogue about developing a vaccine monitoring framework in the EU environment coordinated by the EMA and ECDC.

Introduction

The importance of infectious disease surveillance and related vaccine performance monitoring (effectiveness, impact) in near real time has been on the spotlight again with the COVID-19 pandemic but was already strengthened after the 2009 H1N1pdm09 influenza pandemic. To support this, a well-established network/infrastructure is necessary in order to generate post-authorisation Real-World Evidence (RWE, (1)) and to continuously monitor disease evolution, virus circulation, vaccine coverage rates, and vaccine Benefits/Risks (B/R) in an extended population. Moreover, multi-stakeholder collaboration to control infectious diseases and mitigate their consequences with the development of vaccines and vaccination programmes implementation is crucial. Bringing together the expertise and knowledge of various stakeholders and the complementarity and resource sharing are major benefits gained in a public-private partnership (PPP). These PPPs should be scaled up, when needed, and able to sustain RWE infrastructure.

The Innovative Medicines Initiative (IMI, https://www.imi.europa.eu) is the world's largest PPP in the life sciences. Created in 2008, this European Union PPP is funding health research and innovation through multi-stakeholder projects, with 5 billion euros to date engaged in the period 2008-2022 (half coming from the European Commission (EC) and half coming from the European Federation of Pharmaceutical Industries and Associations (EFPIA)). The IMI provides an adequate framework to pursue public-private collaborations in Europe: public and private experts working together thanks to an established transparent governance. Since 2011, a few IMI projects have been selected to promote collaboration in vaccine post-authorisation setting, where there is a joint interest and mandate of public health institutes (PHIs) and vaccine companies to continuously monitor vaccination programme implementation and vaccines performance. The Accelerated Development of Vaccine benefit-risk Collaboration in Europe (ADVANCE) project was the first addressing that with a methodological perspective. Set up in 2013, this 5-year project (https://www.imi.europa.eu/projects-results/project-factsheets/advance) succeeded in establishing a framework to tackle the challenges that both public and private sectors are facing in the generation of RWE. ADVANCE brought together several key players in the European landscape of vaccine post-authorisation activities, such as the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC), national and regional PHIs, academia, small-medium enterprises (SMEs) and vaccine companies. The project developed best practice guidance, methods, tools, and capacity to generate rapid B/R evidence on vaccines from existing healthcare data, while it also proposed governance principles and different scenarios to develop efficient, transparent and trustworthy public-private collaborations (2, 3) and a code of conduct for studies (4). The participation of the EMA and ECDC in ADVANCE showed the importance perceived by those EU institutions of establishing a robust RWE collaborative infrastructure in the EU for vaccine monitoring.

In July 2016, the EMA published the 'guidelines on influenza vaccines' (5), covering clinical and non-clinical requirements of both seasonal and pandemic influenza vaccines, in which influenza vaccine effectiveness (IVE) studies requiring annual assessment by vaccine brand were included as one of the clinical requirements. This reflected the increased desire from regulators to obtain post-authorisation yearly vaccine performance estimates as part of their routine B/R

assessment. However, obtaining robust IVE estimates per brand is a significant challenge for several reasons. Firstly, many influenza vaccines are developed with various technologies (6), and several brands are licensed in Europe (e.g., 12 brands in 2021-22); however, brand information is not often captured in healthcare systems and/or electronic medical records. Secondly, the distribution of seasonal influenza vaccines in Europe is difficult to predict, as this is an annual process with tenders in some areas or other vaccine procurement processes and with non-harmonised timing (7), which makes timely site selection for setting IVE studies more difficult. Finally, the estimation of IVE of different brands in different risk and/or age groups requires a large sample size, making this endeavour challenging in a fragmented European market. As a result, to assess IVE by brands, the effectiveness cannot be reliably measured without establishing a large study network to evaluate the various vaccines across countries and settings.

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. In their Feasibility Assessment Report (as communicated to the DRIVE partners by ECDC), I-MOVE acknowledged the challenge of conducting brand-specific and vaccination programme-specific IVE (seasonal and pandemic) in the EU/EEA. I-MOVE emphasised that measuring brand-specific IVE in every season is possible only through a sustainable system in which studies are embedded in existing national and regional influenza surveillance systems.

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. Several discussions occurred between vaccine companies, the EMA and ECDC-I-MOVE, and it was proposed to combine efforts under an adjusted governance. IMI was identified as a convenient pre-existing 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 Vaccine Effectiveness (DRIVE) project was set up in July 2017 to address the challenge of brand-specific IVE evaluation in the EU through a PPP. The DRIVE project included, along 5 years, 16 partners from seven European countries, coming from PHIs, universities, research institutes, SMEs, patients' associations, and vaccine companies (Supplement 1), with a joint interest to advance European cooperation in IVE studies, with a budget of 10 million euros funded equally by EC and EFPIA. DRIVE's main goal was to establish a sufficiently sized network for robust, high-quality, brand-specific IVE estimates for all vaccines used in the EU in each season (8). This proof-of-concept project aimed to develop a sustainable infrastructure for data collection in Europe, providing core protocols for study conduct, methods for pooled analysis, and a governance model for transparent roles and responsibilities between public and private stakeholders. Ultimately, I-MOVE and ECDC 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 evaluation of vaccine effectiveness for

regulatory obligations.

This document summarises the achievements and challenges of the DRIVE initiative and discusses DRIVE legacy and recommendations to sustain collaborative RWE platform in Europe for vaccine effectiveness monitoring.

Results: DRIVE Assets – key components of the collaborative RWE platform

Several components are necessary to ensure a trustworthy, transparent, efficient, robust, and cost-effective RWE collaborative platform to monitor vaccines in the post-authorisation setting.

A large, agile, efficient, and cost-effective study platform

The DRIVE study platform was built on three fundamentals to identify sites that could perform IVE studies using either prospective designs or register-based cohorts: 1) gather existing data leveraging national and regional surveillance systems involved in vaccine monitoring activities conducted by PHI DRIVE partners, 2) optimise the IVE capacity by onboarding other PHIs willing to collaborate with DRIVE to enhance vaccines 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.

In parallel, DRIVE partners also investigated the procurement system, the way vaccine doses are allocated and distributed in the different countries/regions in Europe, to understand seasonal influenza vaccine brand availability in Europe (7). Four main procurement systems were identified across 16 EU countries. Pre-season publicly accessible data on influenza vaccine procurement was limited. Over time, an increasing number of influenza vaccine types had been procured, varying by country. DRIVE partners concluded that the usefulness of procurement data for prospective site selection for brand-specific VE studies is limited. In addition, the challenge of including all brands and reaching sufficient study power to estimate their effectiveness can only be overcome by including multiple countries and a large sample size in each country – effectively 'over-sizing' the network.

The DRIVE study network expanded over the years (Supplements 2-4). Independently operating study sites followed DRIVE core protocols for brand-specific IVE, using either a Test-Negative Design case-control study (9), or a population-based cohort study (10). A statistical analysis plan and a mock report were defined upfront to agree on analysis and results presentation before obtaining data. Data from all study sites were analysed together to increase sample size and geographical coverage in order to capture as many influenza vaccine brands as possible, and a yearly study report encompassing the pooled analysis (stratifying by age, setting and influenza strain) for brand-specific IVE estimations was produced at the end of each season (Supplement 5).

Thanks to an established robust General Data Protection Regulation (GDPR) compliant IT infrastructure and core study documents, the time needed to collect data from the site network, perform the pooled analysis and deliver the seasonal study report has been halved over the 5-year project. The 2021-22 season IVE results were efficiently delivered early July to EMA, two months after the influenza season (end of April), which demonstrates that results could be provided sufficiently timely for public health decision-making.

DRIVE succeeded in establishing a large study platform of pre-existing and new sites, which in the 2021/22 season included 13 sites covering 21 hospitals and more than 1,000 general practices in seven European countries (Spain, Italy, France, UK, Romania, Austria, Iceland) and a nationwide population-based cohort, in Finland.

DRIVE IVE studies were managed in a cost-effective way, especially during the COVID-19 pandemic, allowing to save 17% of the IMI funds (roughly 850k€ from 5 M€ expected for DRIVE IVE studies). From the 2020-21 influenza season onwards, to mitigate the COVID-19 impact and account for the low influenza virus circulation, the sites' study 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.

A transparent public-private mechanism with functioning governance

The DRIVE project was built on the four IMI cornerstones: joint interest (PHIs monitoring their vaccination programme implementations; vaccine companies monitoring their vaccines 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 EC and 5 M€ from EFPIA-split in 1 M€ in-kind contribution and 4 M€ for the IVE studies), and transparent reporting (IVE results submitted to EMA, IMI and available to the scientific community through the DRIVE website and in peer-reviewed journals).

The DRIVE study platform governance fundamentals derived from the ADVANCE guidance and recommendations for post-authorisation vaccines monitoring (3): 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.

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 integrating DRIVE partners and committees' experiences and gathering external stakeholders' perceptions (especially from PHIs) from surveys and workshops.

The DRIVE study platform established a model of collaborative framework with governance boundaries (Supplements 2, 3).

The study documents (core protocols, statistical analysis plan, seasonal IVE report and publication) underwent a thorough and transparent review oversight by an Independent Scientific Committee (ISC, composed of five IVE experts, independent and unpaid for their voluntary contribution). The study documents were developed by the public partners and circulated to ISC and vaccine company partners. Scientific experts from vaccine companies provided written comments on the study documents. The ISC reviewed study documents and adjudicated on comments from vaccine company experts. Data collection was carried out at several independently operating study sites, which constituted the study network. 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. Sites were selected through a public call on a yearly basis, with the advice of the ISC to the DRIVE Steering Committee (with equal representation of DRIVE public and vaccine companies partners). Brainstorming sessions were organised between scientists from both public and vaccine company partners to discuss IVE methods and upfront study document development (led by public partners). A Quality Control and Audit Committee (QCAC, composed of quality assurance experts from vaccine companies) evaluated the quality of the study conduct, data reporting and the pooled analysis from an operational, process and compliance perspectives. They ensured quality standards in line with vaccine companies' regulatory requirements. The resulting quality reports were added to the IVE results seasonal reports and submitted to the EMA.

The DRIVE scientific community pursued methodological investigations, notably exploring the impact of potential confounders on IVE in a multi-country network of sites conducting test-negative design (TND) studies (Stuurman et al. Manuscript under review at Influenza & Other Respiratory Viruses.). Scientists agreed on the use of a parsimonious approach to confounder adjustment, limited to adjusting for age, sex, and calendar time, in network-based TND IVE studies that conduct analyses stratified by age groups and site, and subsequently pooled by age and setting.

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.

DRIVE produced a short video (https://youtu.be/oitLQU2gyI8) 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. Finally, full transparency was ensured by the maintenance of a public website providing the platform governance rules and all study outputs.

Representative and coherent brand-specific IVE estimates

The development of the DRIVE study platform allowed to capture an increasing number of influenza vaccines used in EU, providing IVE results for 67% of the brands in the 2021-22 season (moving from four brands out of the 11 vaccines on the EU market in 2017/18 season to eight out of 12 in 2021-22, Supplement 6). The last (2021-22) season included one brand for trivalent inactivated adjuvanted vaccine (Fluad – Seqirus), one brand for quadrivalent live attenuated vaccine (Fluenz tetra – AstraZeneca), three brands for quadrivalent inactivated egg based vaccines (Vaxigrip tetra – Sanofi, Fluarix tetra – GSK and Influvac Tetra - Abbott), one brand for quadrivalent inactivated cell based vaccine (Flucelvax Tetra - Seqirus), one brand for quadrivalent inactivated adjuvanted vaccine (Fluad tetra – Seqirus) and one brand for high dose vaccine (Efluelda - Sanofi). This reflects the transition in EU vaccination recommendations from trivalent to quadrivalent influenza vaccines and the diversity of the vaccine types (non-adjuvanted/adjuvanted, inactivated/live attenuated, egg based/cell based and standard dose/high dose). In a differentiated vaccine landscape, a strong study platform was key to capture an increasing number of brands and their actual protection.

Considering the two influenza seasons of interest for DRIVE combining virus circulation and sites network capacity in the five-year project (2019-20 as a mild influenza season with an intermediate-sized network of sites, and 2021-22 as a low influenza season and the final sites network), DRIVE gathered data from 9,077 subjects in the TND studies and 511,854 person-years (py) in the population-based cohort for the 2019-20 season and 6,315 subjects and 836,622 py for the 2021-22 season. In 2019-20, more precise brand-specific estimates, below the threshold of confidence interval width < 40% arbitrarily agreed upon by DRIVE scientists, were obtained for three brands of quadrivalent influenza vaccines (Vaxigrip tetra – Sanofi, Fluarix tetra – GSK and Fluenz tetra – AstraZeneca).

Overall, IVE point estimates provided by DRIVE were consistent with those published by other initiatives and stakeholders. However, DRIVE was unique in providing systematically brand-specific IVE results in the EU for each season (compared to vaccine type and overall IVE estimates provided by others). As a matter of fact, for the 2019-20 season, DRIVE point estimates were compared with the EU I-MOVE network for any vaccine against any influenza among children in primary care (DRIVE: 64% [95%CI 44-80], I-MOVE: 64% [95% CI 16-85] and for any vaccine against influenza A among elderly in hospital settings (DRIVE: 53% [95%CI 35-67], I-MOVE: 37% [95%CI 19-50] and 62% [95%CI 41-76]) and found to be similar (11).

The lack or very low level of influenza circulation, partly due to the non-pharmaceutical interventions and lockdowns implemented to address the COVID-19 pandemic (12), and the shift of attention and resources to COVID-19 have severely impacted the 2020-21 season and to a lesser extent the 2021-22 season. All this disrupted DRIVE's goal of generating more robust brand-specific IVE estimates in its last two seasons despite efforts made by sites to minimise the COVID-19 impact on data collection.

A regulatory pathway

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. Vaccine companies in DRIVE had licensed seasonal influenza vaccines under different licensure procedures (i.e., centralised vs de-centralised procedures) and thus had different points of contact and timelines/calendar for their regulatory obligations/submissions. When DRIVE was launched, there was no standard mechanism to reach out to regulatory authorities as a consortium (as opposed to individual Marketing Authorisation Holders (MAH)). Thus, the DRIVE consortium engaged in discussions with the EMA to align expectations for vaccine performance data and reporting from multi–MAHs (i.e., the joint seasonal reports). This facilitated a dialogue to discuss challenges and hurdles in vaccine monitoring implementation and results interpretation, including the expectations from authorities about VE robustness and what they consider informed results for decision-making.

Seasonal reports to the EMA were submitted jointly by the DRIVE consortium to fulfil the regulatory obligations of the vaccine companies involved. For the 2017-18 and 2018-19 seasons, the EMA and the Vaccine Working Party (VWP) concluded that IVE results were insufficient to allow a meaningful discussion with regulators. After the 2019-20 season, DRIVE sought to obtain additional insights from regulators using the National Scientific Advice (via the Paul Ehrlich Institute) on the design and statistical analysis of the IVE studies to adjust, if appropriate, the development of the protocols and analysis for the upcoming influenza seasons. As challenges were still experienced to reach a sufficient sample size to perform all stratified analyses in age groups and settings for all vaccine brands, DRIVE considered focusing on populations with the highest disease burden and relatively high vaccine coverage and limited the required number of confounders to be collected. The EMA/VWP welcomed those DRIVE proposals when reviewing the 2019-20 seasonal IVE results report (review done on 14 December 2020 – ref: EMA/573476/2020) and endorsed continuation of the project.

Transparency and sharing of scientific outputs and communication

Seasonal IVE results reports were made publicly available on the website, discussed with the scientific community during annual forum meetings and submitted to the EMA for regulatory evaluation. 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 (13, 14) and presented at conferences (Stuurman et al., ESCAIDE, 2020; Carmona et al., ESWI, 2021).

Throughout the project, communication experts from DRIVE partners (PHIs, universities, research institutes, vaccine companies and a patients' association) jointly raised awareness of influenza burden and the complexity of accurately evaluating the performance of each brand of influenza vaccine each year. DRIVE communication mainly targeted regulators, governments and DRIVE stakeholders' peers and used several channels and tools (73 website posts, 34 event participations, 26 newsletters and 21 scientific publications). Cooperation with the patient association helped ensure accessibility of the messages. However, DRIVE faced a double challenge: to present IVE and to advocate for PPPs to ensure trust in those results. DRIVE's message on the benefits of PPPs generated RWE for vaccine monitoring deserves to be pursued in the future and adapted after the massive educational campaign derived from the COVID-19 pandemic.

Discussion

DRIVE Legacy for vaccines monitoring environment in EU: Encouraging data-sharing practices

While RWE is playing an increasing role in healthcare decisions (15) and the COVID-19 pandemic may have accelerated open data and access practices (16, 17), 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 (18). Existing data-sharing systems and frameworks are facing many big challenges and problems (19) such as, but not limited to, data standardisation, security, financial support, and communication.

DRIVE's 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 (supplement 7), 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 (20) and respects the legal obligations that were originally defined in the DRIVE IMI consortium agreement.

Joint efforts to tackle COVID-19

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 (CVE) in real-world conditions to complement what is known from clinical trials conducted for marketing authorisations. In addition to overall effectiveness for each brand of vaccine, key areas of interest include duration of vaccine protection, effectiveness against disease caused by newly emerging SARS-CoV-2 strains, effectiveness against severe COVID-19 disease, and effectiveness in special risk groups, such as immunocompromised, frail individuals, or subjects with chronic conditions or existing comorbidities.

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/).

AstraZeneca and Janssen were the first vaccine companies in this partnership to monitor the effectiveness of their respective vaccines starting patient recruitment in September 2021 in Spain. In mid-May 2022, the COVIDRIVE site network comprised 14 active hospitals (Belgium, Austria, Italy, and Spain), which enrolled over 3,300 SARI patients. More hospitals and countries (France, Germany) are expected to contribute to the data collection along with additional vaccine companies' requests.

COVIDRIVE governance bodies are a heritage of DRIVE (same structure while membership differs), including a Steering Committee, an ISC and a QCAC. In COVIDRIVE, efficiency in scientific exchange was improved with the joint development of Master study protocols and statistical analysis plans between scientific experts representing public and private partners, while independence for more sensitive activities like the study conduct, data analysis and CVE results interpretations was kept under public lead and ISC oversight to manage potential conflicts of interest from vaccine companies.

Contrary to the joint brand-specific IVE study conducted in DRIVE (one report containing all partners brands corresponding to a common regulatory requirement for vaccine companies), within the COVIDRIVE partnership, a Master study is conducted by several sites following a Master protocol and distinct brand-specific CVE results reports are produced for each company, to respond to specific regulatory requirements. Presently, sequential submission of COVID-19

vaccines for European marketing authorisations led to distinct regulatory requirements for vaccine companies. However, harmonisation of CVE methods ensured by the development of Master protocol(s) intends to guarantee mutualisation of healthcare providers/site resources in primary data collection. This means that research methods (e.g., study objectives, subject inclusion/exclusion criteria, case definitions, exposures/outcomes and collected data/variables) defined in a Master protocol ensure that data collected by sites can feed several CVE results reports and thus, the study cost is fairly shared between vaccine companies.

COVIDRIVE exemplifies the value of both existing RWE infrastructure and multi-stakeholder collaboration to repurpose a vaccine effectiveness platform under pandemic urgency. The COVID-19 pandemic highlights the need for a public-private collaborative environment to generate vaccine effectiveness data to advise the design of national immunisation programmes and to fulfil the effectiveness requirements established by the regulatory authorities.

Hurdles and potential solutions/alternatives

DRIVE's initial perspective was to establish an EU–wide RWE collaborative platform to generate robust brand-specific IVE for all vaccines, populations, and settings in the EU for informed decision-making. But its key prerequisite of scaling up this proof of concept by recruiting additional PHIs or initiatives experienced in conducting IVE studies to share data and perform pooled analysis was 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 of collecting 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 (12), 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*" (21). 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*" (22).

Consequently, DRIVE public partners efforts made to invite PHIs to collaborate and share surveillance system data were limited to the onboarding 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 existing three PHIs DRIVE partners (THL-Finland, ISS-Italy and FISABIO-Spain). 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), six of them were contacted by DRIVE public partners before the COVID-19 pandemic was announced. Subsequent meetings and discussions occurred, unfortunately resulting in an unsuccessful ending (mixing and/or combining the three main factors listed above).

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 EC 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.

Presenting its lessons learnt and concerns to the EMA, DRIVE partners concluded that in the absence of a clear EU level coordination of stakeholders' roles, responsibilities and investments, the DRIVE platform cannot be sustained beyond this IMI project (ending on June 30th, 2022). The competitive environment for data collection is jeopardising any possibility to generate meaningful IVE data despite joint public and private funding, and thus, would not allow a post–DRIVE initiative to reach its expected level of capacity. The DRIVE consortium has formally requested a deferral to the EMA on the conduct of yearly post-authorisation effectiveness studies for influenza seasonal vaccines. This deferral is intended to help clarify the roles and

responsibilities of each stakeholder including European institutions.

Whereas healthcare resources, expertise, and investments coming from public and private stakeholders could be centralised to build a sustainable and robust RWE infrastructure for disease surveillance and vaccine effectiveness monitoring (at least currently mutualising efforts for two vaccine-preventable respiratory infectious diseases like influenza and COVID-19) it is unfortunate to observe such reluctance to collaboration despite efforts made in governance boundaries, transparency, and data-sharing practices. Cost-sharing principles applied in COVIDRIVE could be adapted to a multi-pathogen infrastructure and thus, support an economy of scale and healthcare resources and joint public and private funding.

Europe has had a history, at least in the field of influenza, of changing VE platforms over time and with some overlaps (with I-MOVE, DRIVE and VEBIS), which may have resulted in lack of continuity and waste of public and private money. While different platforms may address different stakeholders' needs (near real time IVE estimates for PHIs to make and revise policy recommendations for vaccination programmes and robust IVE estimates for regulators to monitor vaccines B/R), it may be of interest to discuss, using DRIVE assets and lessons learnt, how a combined and sustainable approach for vaccine effectiveness platform would be of interest to improve the European surveillance ecosystem collectively.

Conclusion: Prerequisite for a sustainable RWE infrastructure for vaccine monitoring in EU: DRIVE recommendations

As a proof-of-concept, the DRIVE project 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 foundations (CoMO-UK and IABS-EU-France), and vaccine companies (Sanofi-France, GSK-Belgium, Seqirus-The Netherlands and Abbott-The Netherlands)
- a large study platform, including 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 on the EU market (8 out of 12 vaccines)
- A trusted public-private collaborative platform where IVE point estimates were consistent with those published by other initiatives and stakeholders
- 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 (six requests already proceed)
- a viable approach to repurpose a vaccine effectiveness platform under COVID-19 pandemic urgency (COVIDRIVE was set up in 9 months)

The recent change in the European vaccine ecosystem combined with the existing complexity, in terms of disease surveillance, vaccines development and delivery, immunisation programs implementation and monitoring of vaccine performance and interconnection between several stakeholders in Europe should strive for the best possible coordination to ensure that EU citizens benefit from joint capacities. The DRIVE partners are of the opinion that a debate on the benefits of PPP generated RWE for vaccine effectiveness monitoring should be foreseen to clarify roles and responsibilities, set up the expectations and decide the future environment for vaccine monitoring. 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.

DRIVE partners are convinced that public-private collaboration should be foreseen to sustain a cost-effective RWE infrastructure in the EU for vaccine effectiveness monitoring. They hope that considerations will be given to the DRIVE public private collaborative model in the ongoing dialogue about developing a vaccine monitoring framework in the EU environment coordinated by the EMA and ECDC.

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Supplementary materials

FISABIO (Spain)

Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana

ABBOTT (Netherlands)

Abbott Biologicals

IABS-EU (France)

Association Internationale de Standardisation Biologique pour L'Europe

CoMO (United Kingdom)

Confederation of Meningitis Organisations

GSK (Belgium)

GlaxoSmithKline Biologicals

ISS (Italy)

Istituto Superiore di Sanità

THL (Finland)

Finnish Institute for Health and Welfare

P95 (Belgium)

Excellence in Pharmacovigilance and Epidemiology

SP (France)

Sanofi Pasteur

SEQIRUS (UK)

A CSL Company

SYNAPSE (Spain)

Synapse Research Management Partners

UNIFI (Italy)

Università degli Studi di Firenze

UCBL (France)

Université Claude Bernard

OXFORD (United Kingdom)

University of Oxford

INSERM (France)

Institut national de la santé et de la recherche médicale

OPBG (Italy)

Ospedale Pediatrico Bambino Gesù

Supplement 1. DRIVE consortium members (as of 2022)

Public partners:

Finnish Institute for Health and Welfare (THL), Finland

Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (Fisabio), Spain

Institut national de la santé et de la recherche médicale (Inserm), France

International Alliance For Biological Standardization – European Affiliate (IABS-EU), France

Istituto Superiore di Sanità (ISS), Italy

Ospedale Pediatrico Bambino Gesù (OPBG), Italy

Universita Degli Studi Firenze (UNIFI), Italy

Université Claude-Bernard Lyon 1 (UCBL), France

University of Oxford, United Kingdom

Small and medium enterprises (SMEs):

P95 Epidemiology & Pharmacovigilance, Belgium

Synapse Research Management Partners, Spain

Vaccine companies:

Abbott, the Netherlands

GSK, Belgium

Sanofi, France

Seqirus, United Kingdom

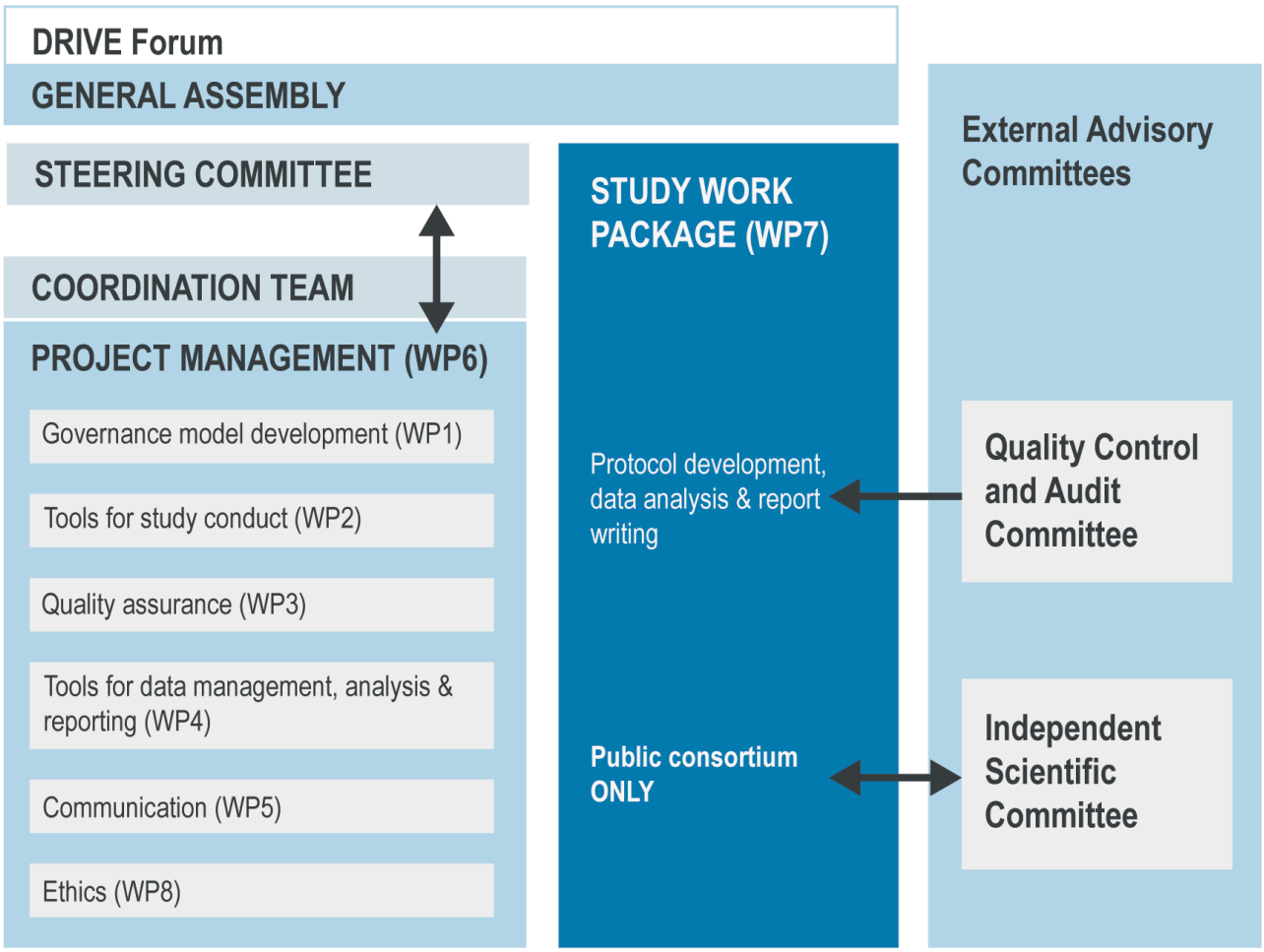
Patients' association:

Confederation of *Meningitis* Organisations (*CoMO*), United Kingdom

FISABIO is the DRIVE coordinator and Sanofi is the EFPIA lead.

DRIVE received funding from the IMI2 Joint Undertaking under grant agreement No 777363, equally split between the EU Horizon 2020 program and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The DRIVE total budget was 10 million euros over the 5 years, 50% coming from EC and 50% coming from EFPIA members (including 1 million in-kind from EFPIA and 4 million financial from EFPIA).

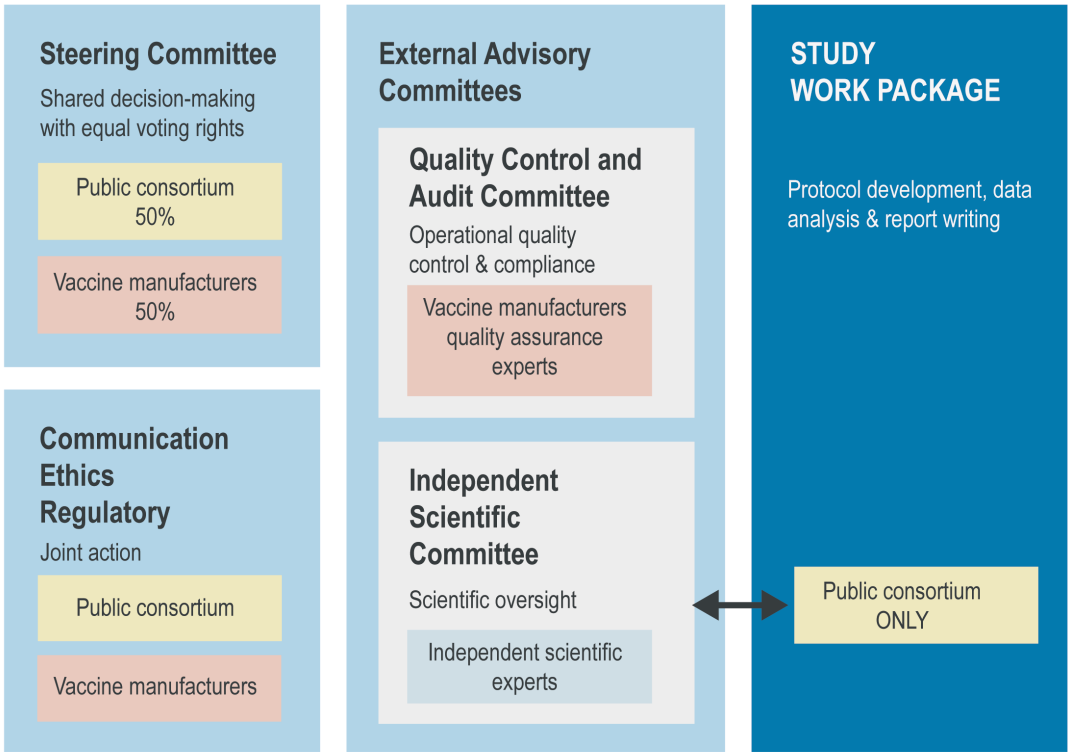
Supplement 2. DRIVE structure and governance.



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.

Supplement 3. Working groups supporting the DRIVE study platform for brand-specific IVE studies.

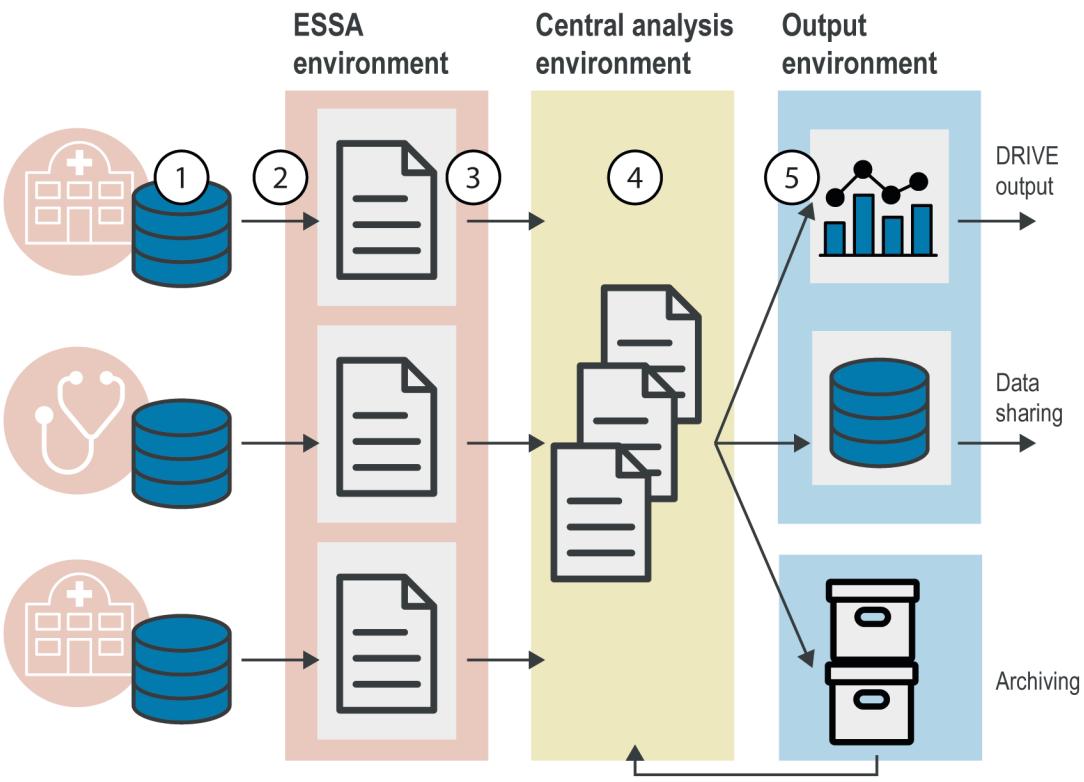


The established governance ensures that brand-specific IVE studies are scientifically robust, independently conducted and that they enable partners to fulfil their missions and obligations:

- The Steering Committee decides on the study platform's strategic direction, allocations of funds and resources for the IVE studies. The steering committee is composed of representatives from the DRIVE consortium. Decision authority is split equally between the public consortium and the vaccine companies.
- Study documents (protocols, statistical analyses, reports and publications) are developed by scientific experts from public partners. Scientific experts from vaccine companies' partners provide written comments on the documents to the Independent Scientific Committee (ISC) who reviews the documents for comment and adjudication. The ISC is composed of five independent experts in the field.
- The Quality Control and Audit Committee (QCAC, composed of quality assurance experts from vaccine companies) evaluates the quality of the study conduct, data reporting and the pooled analysis from an operational, process and compliance perspective. They ensure high data quality standards in line with industry regulatory requirements. Audits are performed by a third party under QCAC oversight when needed.
- Data collection is carried out at several independently operating study sites which constitute the study network (Supplement 5). FISABIO as DRIVE coordinator is the sponsor of the IVE studies. Sites remain owners of their data. Vaccine company partners are not permitted access to the data or involvement in the conduct of the studies.

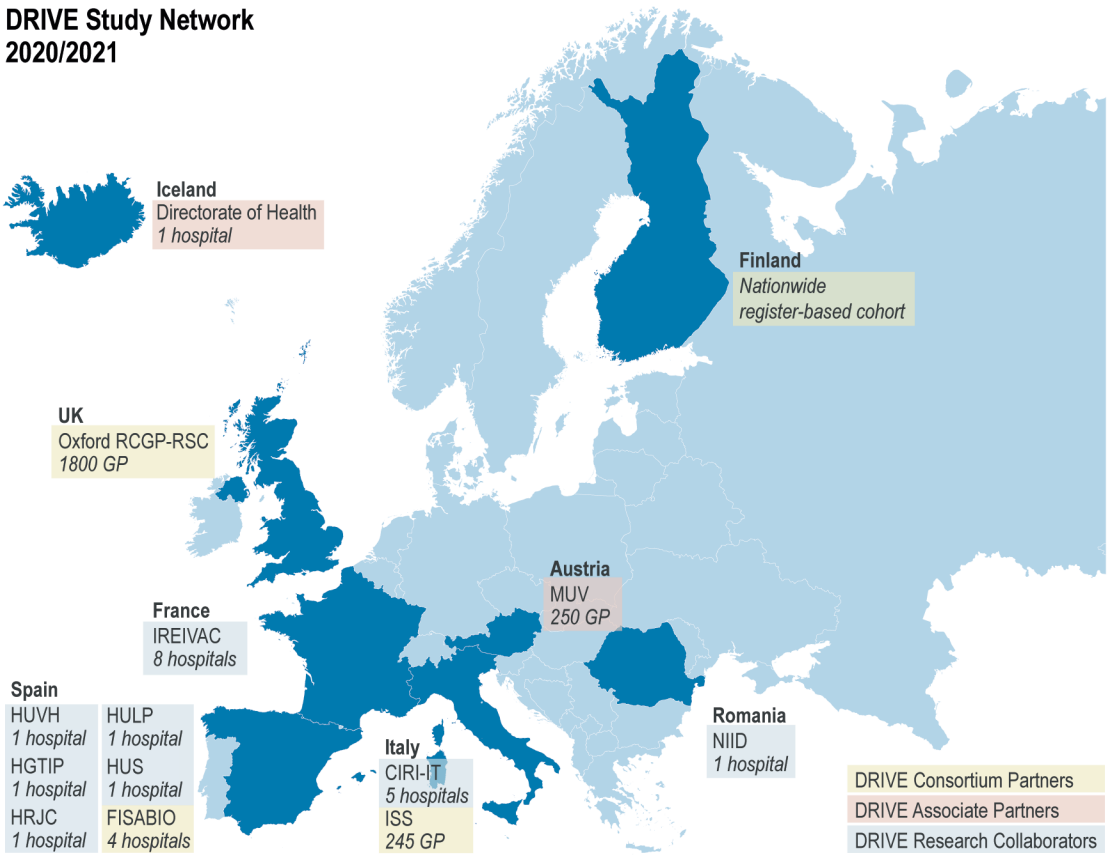
  The study network is composed of DRIVE's original public partners, associate partners (new PHIs who decided to join the project to share data from their surveillance systems) and research collaborators who are selected jointly by the ISC and SC through a public call on a yearly basis to conduct brand-specific IVE studies.

Supplement 4. DRIVE data flow



- This GDPR-compliant infrastructure guarantees access security, data quality controls, efficient pooled analysis, and outputs customisation.
- The infrastructure uses a modular compartmentalised design for easy scale-up and data sharing.
- Sites prepare data following DRIVE Minimum dataset requirements (defined in the core study protocols).
- Secure data upload is done by site through the DRIVE Electronic Study Support Application (ESSA), a web-application with controlled access through user authentication; it includes multiple functionalities like automated data quality control, data visualisation and a monitoring tool.
- Data are stored in the ESSA environment, and data privacy is checked.
- Data are analysed in a central analysis environment which ensures controlled access to statisticians.
- Tabular and graphical summaries are moved to Export environment.

Supplement 5. DRIVE Study network for season 2021-22



The DRIVE network is composed of (1) 13 independent study sites across Europe that conduct Test-Negative Design (TND) prospective studies (which include a total of 24 hospitals and more than 500 GP) and (2) a nationwide register-based cohort study in Finland.

Supplement 6. Evolution of the DRIVE studies in the last influenza seasons (2019-20 to 2021-22)

Influenza season	2017/18	2018/19	2019/20	2020/21	2021/22
Characteristics	High flu circulation	Moderate flu circulation	Moderate flu circulation – study capped due to COVID-19 emergence	No flu circulation – COVID-19 pandemic	Very low flu circulation – late flu epidemic peak (Mar-Apr 2022) Omicron COVID-19 pandemic
Study network	5 sites 4 countries +950 GP 4 hospitals	10 sites 7 countries 377 GP 12 hospitals	14 sites 8 countries 388 GP 19 hospitals	14 sites 8 countries +500 GP 25 hospitals	13 sites 8 countries +1000 GP 21 hospitals
Number of subjects	5.475 (TND) 288.655 py cohort Finland	9351 (TND) 768.414 py cohort Finland	9.077 (TND) 511.854 py cohort Finland	7.025 (TND) 857.095 py cohort Finland	6315 (TND) 836.622 py cohort Finland
Number of LCI	2.844 (TND) 13.300 (cohort Finland)	3339 (TND) 6379 (cohort Finland)	> 3.500 (TND) > 2400 (cohort Finland)	4 (TND) 25 (cohort Finland)	1046 (TND) 331 (cohort Finland)
Brand-specific IVE estimates	Yes, 4/11 but pilot season	Yes, 7/10 influenza vaccine brands	Yes, 8/11 influenza vaccine brands	No	Yes, 8/12 flu vaccine brands

GP – general practitioner; IVE – influenza vaccine effectiveness; LCI - Laboratory confirmed influenza; py – person years; TND – test-negative design

Supplement 7. Supplementary DRIVE materials

Supplementary videos can be found on the DRIVE website: https://www.drive-eu.org/index.php/governance/

The DRIVE Generic Test-negative Design and Finnish Register-based cohort protocols can be found on the DRIVE website: https://www.drive-eu.org/index.php/results/deliverables/

The DRIVE study results reports can also be found on the DRIVE website:

Season 2017-18: https://www.drive-eu.org/index.php/results/results-2017-18-season/

Season 2018-19: https://www.drive-eu.org/index.php/results/results-2018-19-season/

Season 2019-20: https://www.drive-eu.org/index.php/results/results-2019-20-season/

Season 2020-21: https://www.drive-eu.org/index.php/results/results-2020-21-season/

DRIVE D1.3 Final governance report: to be posted in DRIVE website.

COVIDRIVE:

Press release: COVIDRIVE consortium. New public-private partnership COVIDRIVE to assess brand-specific COVID-19 vaccine effectiveness in Europe. Available at: https://covidrive.eu/2021/07/19/new-public-private-partnership-covidrive-to-assess-brand-specific-covid-19-vaccine-effectiveness-in-europe/

Website: https://covidrive.eu

Supplement 8 – 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].
- 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

[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

	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.

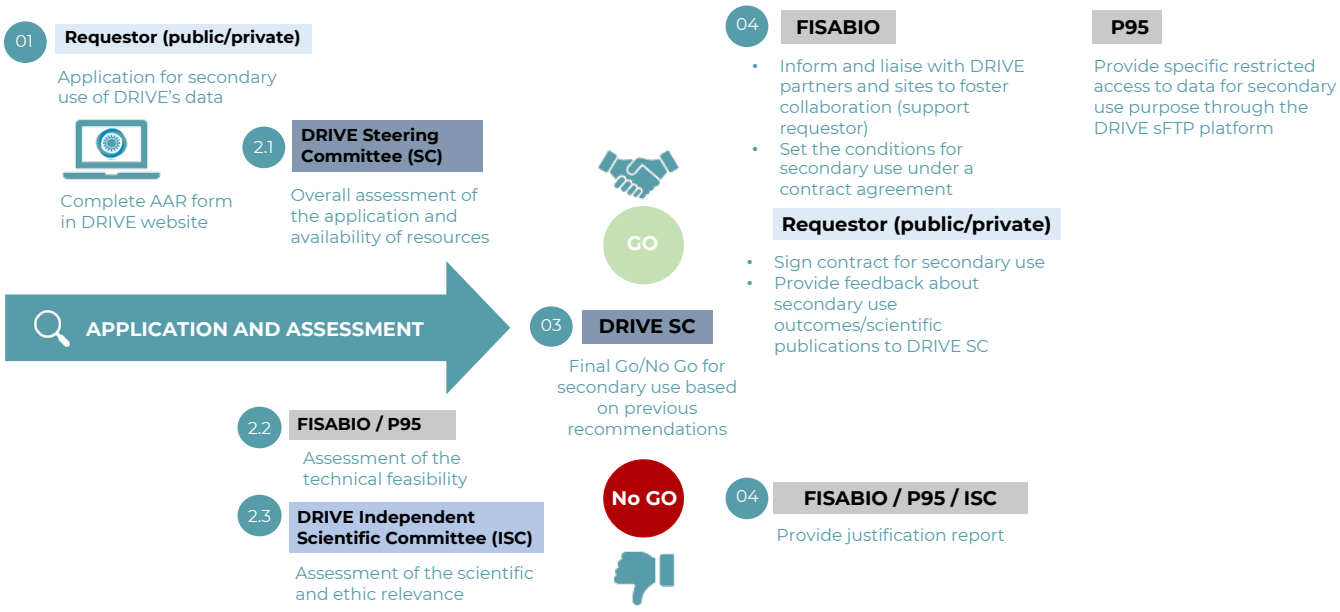


Figure 1: Process for assessing DRIVE use of secondary data.

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]
- 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

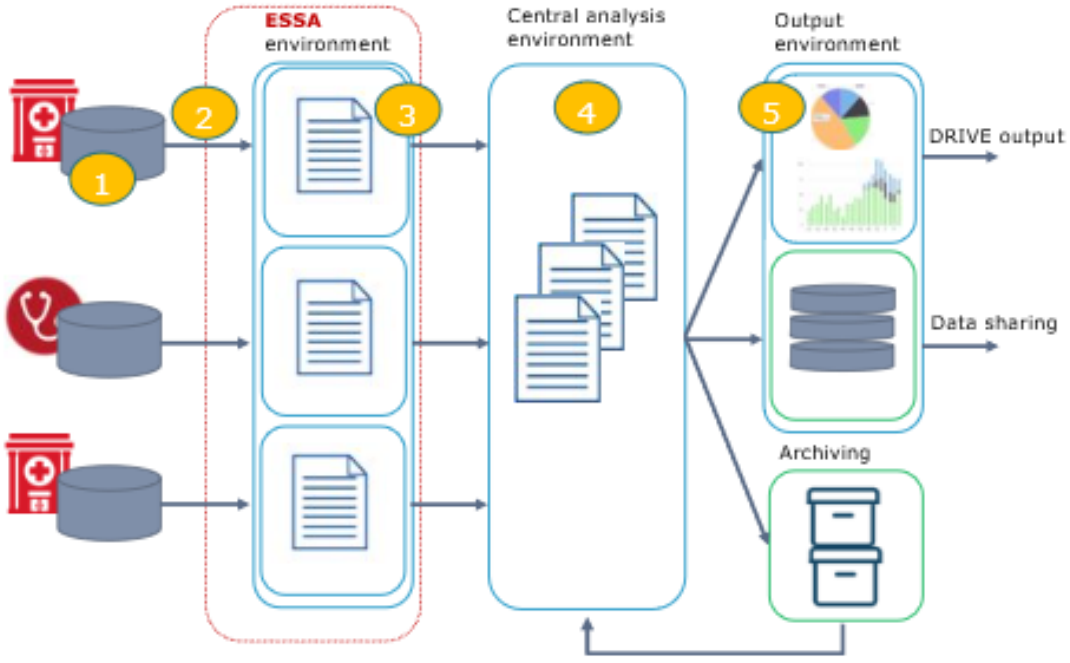

Figure 2: DRIVE data flow

[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