IMI2 777363 – DRIVE

Development of Robust and Innovative Vaccine Effectiveness

WP6 – Project management,

coordination and sustainability

D6.5 Final Report and Sustainability Plan

Lead contributor	Antonio Carmona (1 – FISABIO)
Other contributors	Laurence Torcel-Pagnon (12 – SANOFI)
	Nina Coll (5 – SYNAPSE)
	Clarisse Demont (12 – SANOFI)
	Cintia Muñoz Quiles (1 – FISABIO)
	Valle Morales Cuenca (1 – FISABIO)

Document History

Version	Date	Description
V1.0	5 April 2022	First Draft
V2.0	15 May 2022	Implemented comments DRIVE Coordination team (first round)
V3.0	29 June 2022	Final Version

Table of Contents

Abstract

To enable the development of a study network of Influenza Vaccines Effectiveness (IVE) studies, DRIVE developed a transparent governance model to allow the collaboration of different stakeholders, through a public-private partnership (PPP). DRIVE kicked-off in July 2017, aiming to build a wide study platform able to generate robust, high quality, brand-specific effectiveness estimates for influenza vaccines in the EU. The data generated through DRIVE aimed to increase the understanding of influenza vaccine effectiveness in Europe, leading to enhanced monitoring of influenza vaccine performance by Public Health Institutes (PHIs). Moreover, the platform was designed to allow manufacturers to fulfil their regulatory requirements by annually submitting DRIVE IVE Results reports to the European Medicines Agency (EMA).

In summary, DRIVE succeeded in setting up a multi-stakeholders PPP for Real World Evidence (RWE) assessment of IVE, based on a large, robust, agile, efficient and cost-effective study site platform. DRIVE has ensured transparent and fruitful scientific collaboration between public and private partners and setting governance boundaries.

This report, led by FISABIO with the collaboration of all DRIVE Work Package (WP) leaders, summarizes the key achievements, lessons learned, challenges and improvements made during the 5 years of the project. Moreover, it also describes how the WP6 has dealt with the day-to-day management and scientific coordination of the project, and how the operational aspects of the DRIVE sustainability plan have been shaped.

Abbreviations

AAR	Additional Analysis Request
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ESSA	Electronic study support application
EU	European Union
HERA	European Health Emergency Preparedness and Response Authority
IMI	Innovative Medicines Initiative
ISC	Independent Scientific Committee
IVE	Influenza Vaccine Effectiveness
LCI	Lab-confirmed influenza
MoU	Memorandum of Understanding
PHI	Public Health Institute
PPP	Public-Private Partnership
py	Person-years
QCAC	Quality Control and Audit Committee
RSV	Respiratory Syncytial virus
RWE	Real-World Evidence
TND	Test-Negative Design
VE	Vaccine Effectiveness
WP	Work Package

Summary of DRIVE achievements through the years

DRIVE: lessons learnt and achievements

DRIVE is a 5-year project funded under the Innovative Medicines Initiative (IMI). The project kicked off in 2017 and is run by a consortium composed of 16 public and private partners, who joined efforts with the aim of establishing a sustainable study platform based on a sufficiently sized network to provide robust, high quality, brand-specific effectiveness estimates for all influenza vaccines used in the EU each season. In DRIVE, data from several independently operating national or regional study sites is analyzed jointly to increase geographical coverage and sample size for brand-specific influenza vaccine effectiveness estimates and account for various vaccinations recommendations and uptakes.

Several components are needed to ensure a trustworthy, transparent, efficient, and cost-effective Real-World Evidence (RWE) collaborative platform to monitor vaccines in a post authorization setting:

- A transparent public-private mechanism with functioning **governance**: built on joint interest, shared decision making, joint funding, and transparent reporting; multi-stakeholders' approach for collaboration in methods; definition of clear roles and responsibilities among stakeholders; processes in place to manage perception of conflict of interest; guaranteed independence of the study conduct (driven by public partners for data collection and analysis); independent scientific experts who advise on study documents, review study results and adjudicate on conflicting results interpretations, high data quality standards with documentation and traceability, (based on industry quality assurance standards); full transparency ensured by a public website, sharing platform governance rules and study outputs.
- An agile, efficient, and cost-effective **study platform**: independent study sites following generic protocols using both prospective designs and register-based cohorts built on national or regional surveillances, a public call for site applications and selection based on experience/expertise of the sites and gaps analysis for a targeted approach, study documentation with statistical analysis plan defined upfront, mock report to agree on results presentation before getting data, GDPR-compliant IT infrastructure for efficient and compliant data collection and pooled analysis (with appropriate pooling, taking into account age, setting, outcome).
- A **regulatory pathway**: engagement in discussions with EMA to align upfront on expectations for vaccine performance evaluation and expected reporting from multi-Marketing Authorization Holders (e.g., joint report). This facilitates a dialogue to discuss shared challenges and hurdles in vaccine monitoring implementation and results interpretation, including the expectations from authorities about VE robustness and what they consider as informed results for decision making.
- **Transparency** and **dissemination of scientific outputs**; scientific results should be made publicly available and discussed with the scientific community and regulatory authorities for evaluation. It is important to communicate well about VE (what does it mean, why it is variable, the limitations of the estimates, etc.), to come to a common approach to reassure the public about vaccination.

This is further developed in two DRIVE deliverables: D1.3 "Final report on governance and principles" and D1.4 "Real-World Evidence infrastructure for vaccine monitoring in Europe. From proof of concept to sustainability" and in the manuscript recently submitted to Expert Reviews in Vaccines journal "The value of public-private collaborative Real-World Evidence platforms to monitor vaccine performance post authorization: DRIVE - a European initiative" by Díez-Domingo et al (currently in peer review process).

Study platform and influenza vaccine effectiveness

DRIVE has developed a central platform for data collection and analysis, supported by a study network that has expanded over the years (Table 1). Independently operating study sites (selected through a public call for tenders) and associated National Public Health Institutes follow DRIVE core protocols for brand-specific Influenza Vaccine Effectiveness (IVE), using either a Test-Negative Design (TND) case-control study, or a population-based cohort study. Data are analyzed jointly to increase sample size and geographical coverage to capture as many influenza vaccine brands as possible. The annual study report, encompassing the pooled analysis for brand-specific IVE estimations, is produced at the end of each season.

The DRIVE study platform has progressively grown since its first pilot season (2017/18), and in its final 2021/22 season, successfully included 24 hospitals and more than 700 general practices in eight European Union (EU) countries, as well as one nationwide population-based cohort, in Finland (Figure 1). DRIVE obtained its best results in the 2019/20 season, in which the DRIVE study yielded brand-specific influenza vaccine effectiveness estimates for eight of the eleven vaccines available in the European market.

However, the minimal influenza virus circulation, partly due to the non-pharmaceutical interventions and lockdowns implemented to fight the COVID-19 pandemic, together with the shift of attention and resources from influenza to COVID-19, have largely impacted the 2020/21 and 2021/22 seasons, preventing DRIVE from generating robust brand-specific influenza vaccine effectiveness estimates.

Table 1: Evolution of the DRIVE studies in the last influenza seasons (2017-18 to 2021-22). GP – general practitioner; TND – test-negative design

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 for 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, 8/13 flu vaccine brands

DRIVE's main objective in its **first pilot season (2017/2018)** was to establish and test the feasibility of

the new multi-country platform using a limited number of sites. In the following two seasons, an IT platform for data collection was developed jointly by the WP4 partners (and led by P95), protocols and statistical analysis plan were improved and assessment of IVE results and site selection by the Independent Scientific Committee was fine-tuned to ensure transparency.

TND case-control studies (4 in primary care and five in hospital) were conducted in six countries in Europe during the 2018/19 season. Site-specific confounder-adjusted VE estimates for any vaccine exposure were calculated by age group (<18 years (y), 18-64y and 65 + y) and pooled by setting (primary care, hospital) through random effects meta-analysis. In addition, one population-based cohort study was conducted in Finland. TND studies included 3339 cases and 6012 controls; seven vaccine brands were reported. For ages 65 + y, pooled VE against any influenza strain was estimated at 27% (95%CI 6-44) in hospital setting. Sample size was insufficient for meaningful IVE estimates in other age groups, in the primary care setting, or by vaccine brand. The population-based cohort study included 274,077 vaccinated and 494,337 unvaccinated person-years, two vaccine brands were reported. Brand-specific IVE was estimated for Fluenz Tetra (36% [95%CI 24-45]) for ages 2-6y, Vaxigrip Tetra (54% [43-62]) for ages 6 months to 6y, and Vaxigrip Tetra (30% [25-35]) for ages 65 + y. These results are from the second influenza season covered by the DRIVE network. While sample size from the pooled TND studies was still too low for precise (brand-specific) IVE estimates, the network has approximately doubled in size compared to the pilot season. The detailed reports are available in DRIVE website and the results from 2018/2019 season were open access published in Vaccine: DOI: 10.1016/j.vaccine.2020.07.063.

For the 2019/20 season, 4 primary care-based TND studies (Austria, England, Italy), 8 hospital-based TND studies (Finland, France, Italy, Romania, Spain) and one register-based cohort study (Finland) were conducted. Site-specific TND confounder-adjusted IVE estimates were centrally calculated and pooled through meta-analysis. A parsimonious set of confounders was used to simplify the analysis. Moreover, the COVID-19 outbreak impacted influenza surveillance; thus, the study period was truncated on February 29, 2020. In 2019/20, DRIVE estimated IVE for 8 out of 11 vaccine brands available in the market in Europe and obtained the first precise brand-specific estimates from TND studies. Four precise estimates were obtained, two were for any vaccine, and two were brand-specific. Additionally, precise brand-specific estimates were obtained from the register-based cohort study for the two vaccines used in Finland. All these estimates showed a protective effect of influenza vaccination. Despite the challenges faced during the COVID-19 outbreak, the low case numbers in this relatively mild influenza season and low vaccine coverage in certain age groups, DRIVE obtained several precise brand-specific IVE estimates for the 2019/2020 season.

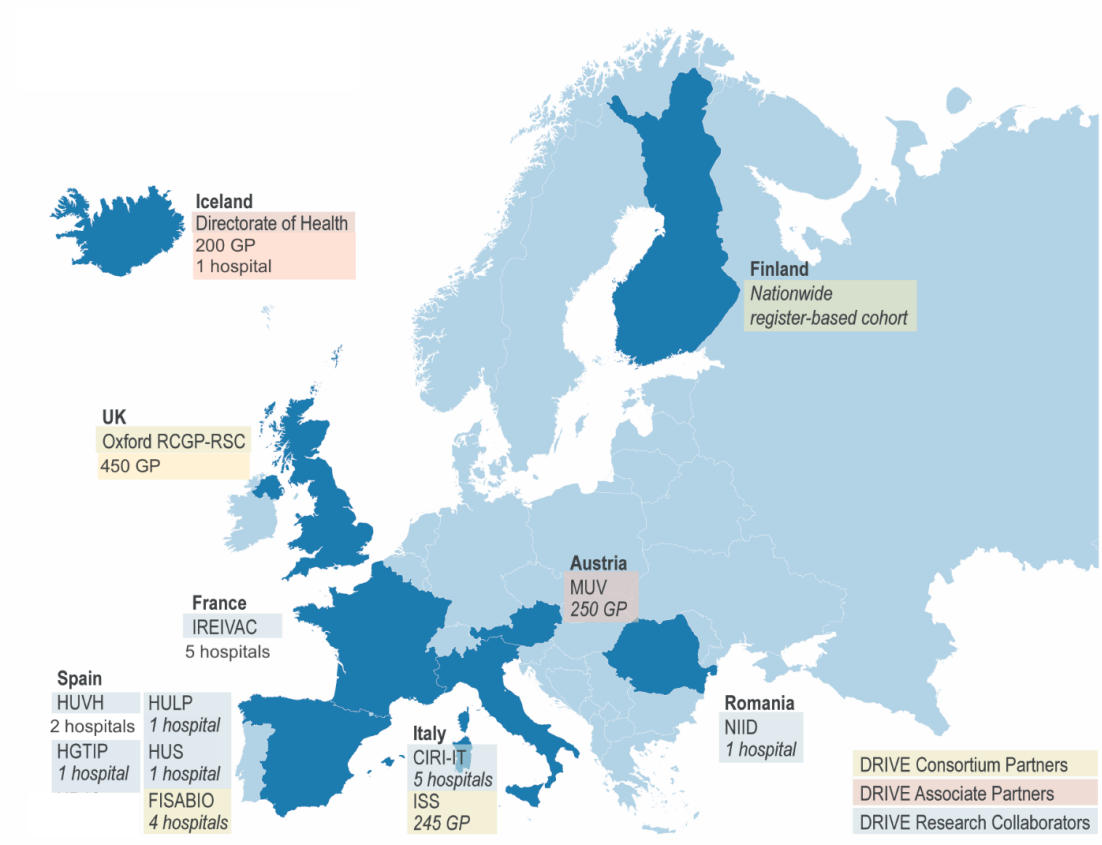
For the 2020/21 season, DRIVE faced its fourth influenza season with the uncertainties posed by the COVID-19 pandemic and the unforeseen changes in the influenza circulation patterns. An expanded study network involving 14 sites in 8 European countries, covering 24 hospitals and more than 500 general practitioners worked together to collect the data necessary for the DRIVE studies and adapt to the particularities of the season 2020/21. In a season marked by the absence of influenza circulation in Europe, the objectives of DRIVE for the 2020/21 season have only been partially fulfilled, as not enough lab-confirmed influenza cases were recruited in DRIVE dataset. Thus, no brand-specific or overall IVE estimates could be obtained for the TND studies, and only overall IVE estimates for the Finnish cohort study were produced. However, the latter could not be interpreted due to large confidence intervals. Nevertheless, DRIVE has conducted a descriptive analysis of the data collected by the DRIVE study sites during the 2020/21 season. Nine influenza vaccine brands were marketed in the EU/EEA/UK in the 2020/21 season. DRIVE dataset has captured 7 out of these 9 marketed brands, demonstrating DRIVE's

ability to gather information on multiple influenza vaccine brands across Europe.

In its final **2021/22 influenza season**, 13 sites from 8 different European countries, covering 21 hospitals and approximately 1125 GP for the TND studies and 1 nation-wide register-based cohort study in Finland (Figure 1) participated in the DRIVE study. Low influenza circulation (in comparison to pre-pandemic flu seasons) was observed, and the flu season was influenced by several factors: 1) interference with the Omicron variant COVID-19 pandemic wave from November 2021 to February 2022 and 2) a late influenza epidemic peak surging in many European countries in March-April 2022. Despite the low influenza circulation, the DRIVE study was conducted smoothly and brand-specific IVE estimations were obtained for 8 out of the 13 influenza vaccines marketed in Europe in the season 2021/22 (and 9 out of 13 were captured in the dataset). This highlights the ability of the study network to cover the variety of influenza vaccine brands administered in Europe. DRIVE was not able to reach the sample size required to produce precise brand-specific estimates due to the low influenza circulation in Europe and the inability to expand the study site network in the current context. Thus, the majority of the IVE estimates were presenting very wide confidence intervals and consequently have to be interpreted with caution.

Annual detailed reports are available for download in the project website: https://www.drive-eu.org/index.php/results/

Figure 1: 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.



In 5 seasons (2017 to 2022) DRIVE included more than 35.000 patients, collecting approximately 60 variables and encompassing 13 different influenza vaccines. DRIVE consortium partners consider that this extremely valuable database should be leveraged and further utilized for various reasons, notably a strong interest in Research and Development activities for new generation of influenza vaccines and a contribution to the worldwide efforts to enhance global surveillance network for respiratory viruses and associated diseases and monitor related vaccines performance. For this reason, DRIVE developed an Open data research framework that will allow the secondary use of the data generated by the project since the 2018/19 season (DRIVE Open data research proposal can be found as Annex 9 of the DRIVE WP1 deliverable D1.3 *"Final report on governance and principles"*).

DRIVE: Leveraging discussions at the European level to emphasize the added value of PPPs for vaccine effectiveness monitoring

DRIVE study platform has been adapted and finetuned along the years, and its efficiency and trust has been acknowledged by DRIVE stakeholders. In this regard, we can confidently affirm that DRIVE was able to develop a suitable governance framework for high-quality research and vaccine performance evaluation fostering transparent collaboration between public and private partners.

However, DRIVE efforts to overcome the hesitancy around the added value of the Public Private Partnership (PPP) (that is still resilient among National Public Health Institutes and certain European institutions) have been mostly in vain. In the final year of the project, DRIVE consortium has invested in disseminating and communicating the numerous achievements made through this collaborative multi-stakeholder platform and leveraging the discussion with relevant EU institutions and associations of the future model(s) for VE platform. To that aim, DRIVE has sought the guidance and expertise of the policy-oriented communications agency ACUMEN. In the final months of the project, ACUMEN has supported DRIVE in organizing a meeting with the European Commission DG HERA in June 3 2022 and a roundtable with key stakeholders from European Institutions as part of DRIVE final Annual Forum 8th June 2022. Moreover, they have reviewed and updated the Communication Plan towards the immediate post-IMI months, and producing the script for a video to be displayed during the Annual Forum and posted in DRIVE website and social media.

Obtaining the first precise BSIVE for the season 2019-20 was a good sign of the value of PPP model aiming to enhance monitoring of influenza vaccine performance by public health institutes and allow manufacturers to fulfil the requirements of the European Medicines Agency (EMA).

Finally, DRIVE demonstrated the added value of public-private European VE platforms and their potential to be applied to other vaccines post-marketing evaluation, notably against COVID-19, with the inception of **COVIDRIVE,** a PPP for brand-specific COVID-19 vaccines effectiveness evaluation in the EU).

This is further developed in two DRIVE deliverables: D1.3 "Final report on governance and principles" and D1.4 "Real-World Evidence infrastructure for vaccine monitoring in Europe. From proof of concept to sustainability" and in the manuscript recently submitted to Expert Reviews in Vaccines journal "The value of public-private collaborative Real-World Evidence platforms to monitor vaccine performance post authorization: DRIVE - a European initiative" by Díez-Domingo et al. (currently in peer review process).

In parallel, in 2021 DRIVE partners initiated the discussions to devise a suitable sustainability strategy for DRIVE. However, DRIVE's initial plan has been severely impacted by the recent changes in the vaccines monitoring environment (including the creation of VEBIS, a joint EMA/ECDC platform for COVID-19 and influenza vaccine effectiveness monitoring). The current European landscape in vaccines monitoring has undeniably raised multiple pragmatic considerations and it also questions the feasibility of sustaining the DRIVE study platform over the IMI funding period.

Considering the above, the DRIVE consortium has engaged in a dialogue with the EMA and the European Commission to pragmatically discuss the requirements, the feasibility components, the rationale and the value of sustaining the DRIVE study platform after the end of DRIVE as an IMI project. Because of the challenges experienced in DRIVE and the ongoing evolution of the current European environment anticipated in the post-DRIVE setting, DRIVE partners considered that it will be even more challenging to successfully continue this collaborative platform aiming to generate robust effectiveness data for all influenza vaccines and fulfil the regulatory requirement for MAHs. For this reason, DRIVE consortium proposed a deferral on generating brand specific seasonal IVE for the influenza season 2022-23 by submitting a cover letter to EMA on the 10th of May 2022.

The governance model of DRIVE and its Open Data and Secondary Use framework is further developed in the DRIVE WP1 deliverable: D1.3 "Final report on governance and principles".

Overall management of the project

The Project Management Office (commonly referred to as the Coordination Team) is composed by partners FISABIO as Project Coordinator, Sanofi as EFPIA lead and SYNAPSE. Under WP6, these three partners have been responsible for the overall management of the project, providing guidance and leadership capacity to successfully deliver all project activities and deliverables.

The main challenges faced were related to managing the different (and sometimes conflicting) interests, expectations and needs of partners of different nature, managing the perception of external stakeholders towards DRIVE as a PPP (and its consequences for the potential involvement of further PHIs in the project), and ensuring the scientific independence of the study results and, more generally, the work carried out in the framework of the DRIVE project. These particularities have been managed jointly by WP1 and WP6, since the studies' governance and the project governance are deeply interrelated and face common issues in terms of management. Moreover, in the context of the COVID-19 pandemic, the management of the project tasks, timelines and review processes had to be fine-tuned and made flexible to account for the new landscape in influenza surveillance and vaccine effectiveness monitoring.

Moreover, the Coordination Team has been constantly adjusting the roles and functions of DRIVE advisory committees: the Independent Scientific Committee (ISC) and the Quality Control and Audit Committee (QCAC), observing an increase in their engagement with the partnership throughout the years. The Coordination Team has steered the activity of the advisory committees, and as a result, the ISC has greatly contributed in DRIVE sustainability discussions, publication strategy, scientific communication and methods workshop; whereas the QCAC has supported the accommodation of MAHs regulatory obligations to real world study design conducted by independent sites and oversaw the audit of the project's IT infrastructure data collection analysis and report system.

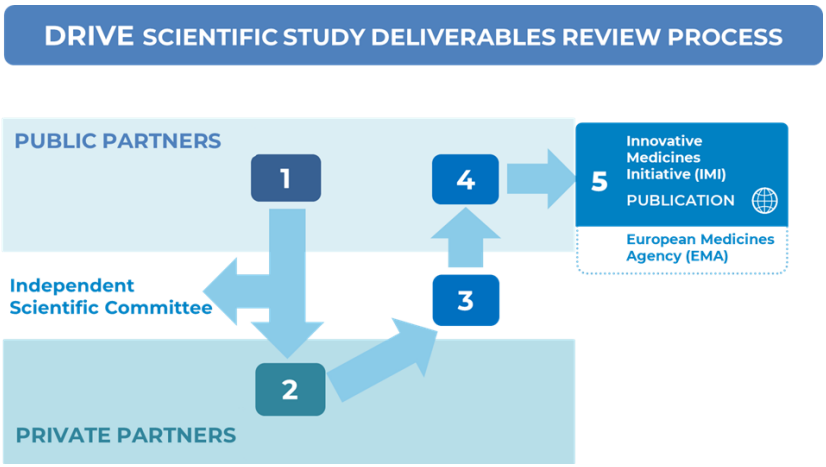
Taking into account the particularities of DRIVE, the following managerial outputs have been achieved:

1. Specific internal procedures

Study documents and reports derived from WP7

The review process of study documents and reports produced in the WP7 has been streamlined through the years with pre-defined timelines and development of "mock" and template reports. The WP7 is in charge of conducting the DRIVE studies and it is only composed of public partners. This independency from the industry is further strengthened through the ISC assessment of the industry comments on study documents and reports (Figure 2). Study documents quality as well as IVE results robustness have been improved over the 4 years thanks to the inputs from all DRIVE stakeholders' scientific experts (WP7, ISC and Vaccine manufacturers).

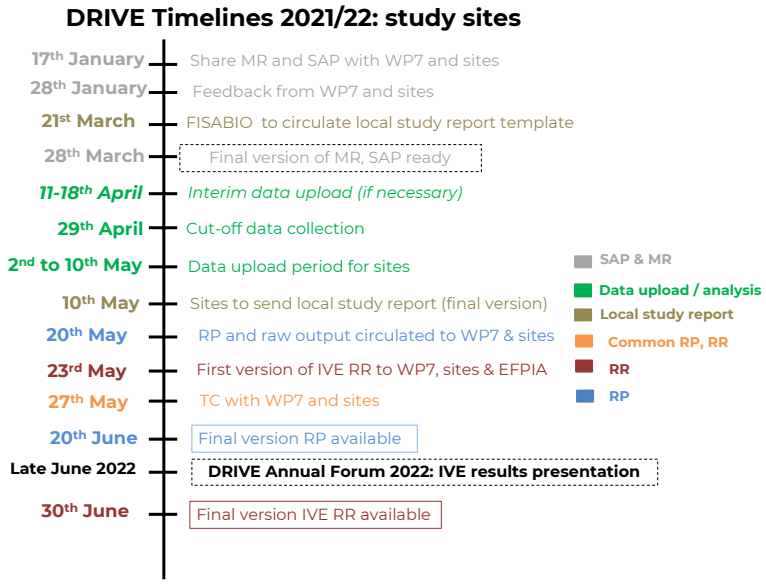
Figure 2: DRIVE review process for WP7 deliverables (study documents and reports). (1) Public partners perform the studies and write the scientific deliverable. The deliverable is circulated to the ISC and the private partners (vaccine manufacturers). (2) Private partners provide written comments to the ISC. (3) The ISC reviews the deliverable, provides comments and marks for inclusion or exclusion private partners' comments. (4) Public partners implement the comments according to the ISC's recommendation and shape the final version of the deliverable. (5) The deliverable is published and submitted to IMI, EMA (in the case of the annual report) and other stakeholders.



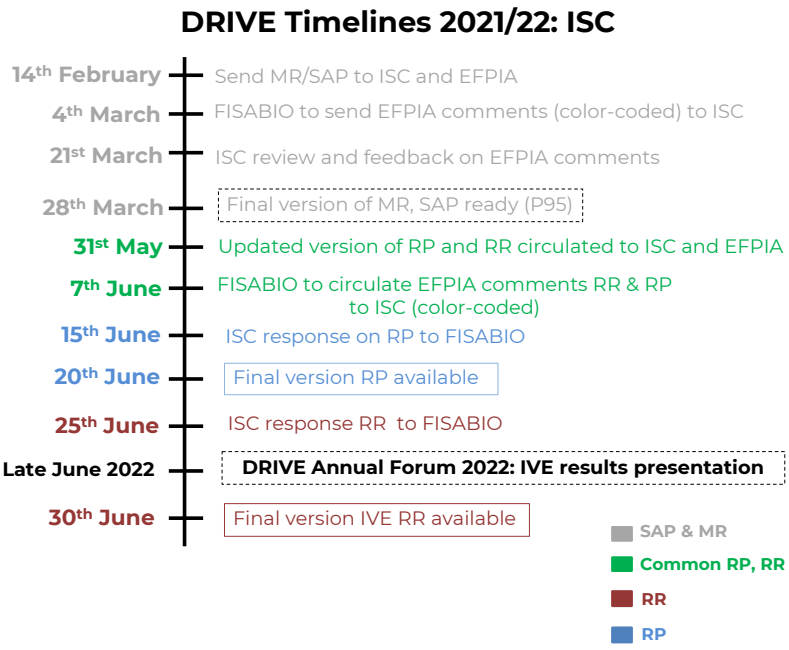
The study timelines were prepared every season by the Coordination Team in collaboration with WP7 and shared with the sites, ISC and DRIVE Steering Committee at the start of the influenza season (Figure 3). With the irruption of COVID-19, and the lack of influenza circulation, the Coordination Team implemented simpler timelines with shorter review processes for the 2020/21 and 2021/22 seasons.

Figure 3: a) Example of timelines for DRIVE sites (2021/22 season) b) Example of timelines for DRIVE ISC (2021/22 season).

a)



b)



Call for tenders and site selection processes and timelines

It was recognised early on that involving additional PHIs and other Research organizations, hospitals or hospital networks in the studies and scientific discussion of DRIVE would be crucial for the success of the project. Thus, in 2018, DRIVE WP2 launched an annual Call for tenders for the season 2018/2019, which has been subsequently launched for seasons 2019/20, 2020/21 and 2021/22.

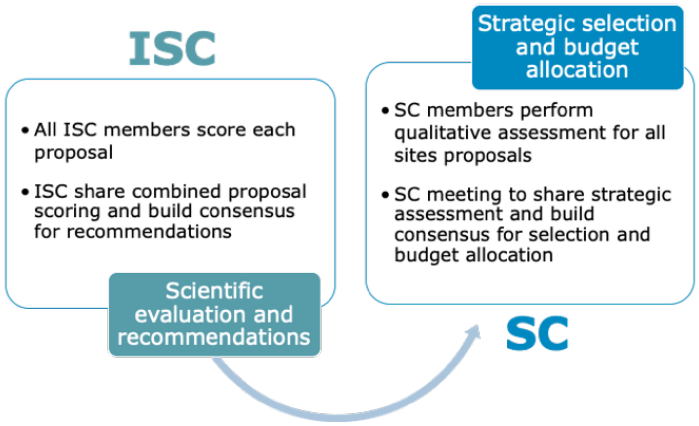
The summary of the Call for tenders and site selection was reported in the WP2 deliverables D2.7 (2018/19), D2.8 (2019/20), D2.9 (2020/21) and D2.10 (2021/22).

The ISC and SC, coordinated by the Coordination Team have been involved in the evaluation of the new studies submitted and selection of the sites participating in the respective influenza seasons. The process has been streamlined through the years:

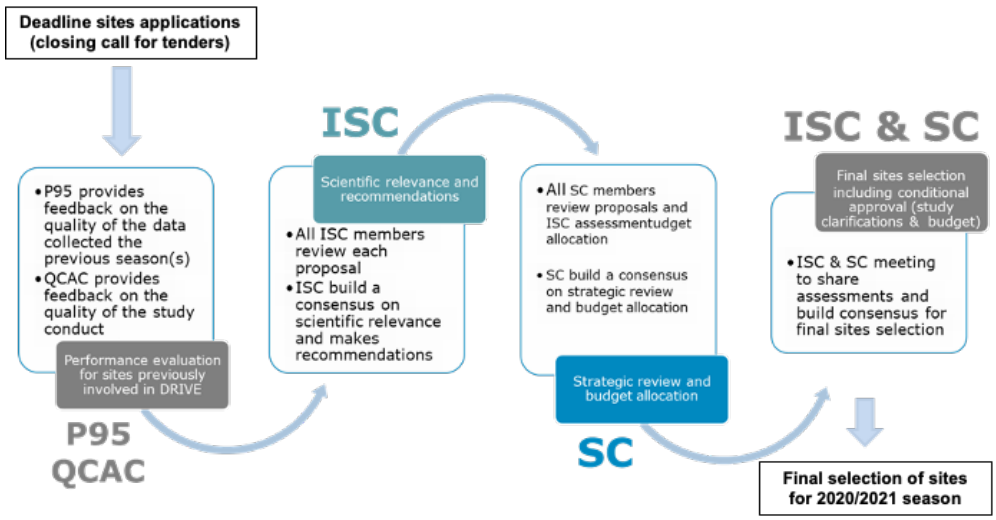
- For the 2018/19 Call for tenders, proposals were reviewed only by the Steering Committee of DRIVE. Each SC member institution scored the proposals using predefined criteria.
- For the 2019/2020 Call for tenders, the sites selection was organised in a stepwise approach coordinated by SYNAPSE and FISABIO (Figure 4 a). In step 1 the ISC performed a scientific evaluation of the sites proposals consisting on a quantitative evaluation, scoring and ranking of the proposals was based on the 5 pre-defined criteria. 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, 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 Steering Committee (SC) for the strategic selection of the sites and allocation of the budget in step 2.

Figure 4: a) 2019/20 Call for tender site evaluation and selection (two stepwise approach) b) From 2019/20 Call for tenders, a three stepwise approach for site selection was implemented.

a)



b)



- **For the 2020/2021** Call for tenders and beyond, the site selection process was adjusted and an extra step was added (3 steps approach, see Figure 4b), coordinated by FISABIO and SP. Changes implemented included:
  - Predefine the scope in the call for tender specifications (inclusion & exclusion criteria).
  - Get feedback on sites that have collaborated the previous season(s).
  - Simplify ISC evaluation criteria.
  - Increase the value of data poolability and sample size contribution.
  - Refine ISC role for final selection of sites.

  In step 1, the QCAC and P95 evaluate 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 on 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 performs 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 meet to share assessments and build consensus for final sites selection, including conditional approval of the proposals.

The final governance model of DRIVE is further developed in the DRIVE WP1 deliverable: D1.3 "Final report on governance and principles".

2. Engagement of National Public Health Institutes

To expand the DRIVE study platform and more specifically its study network (sites able to conduct IVE study), DRIVE partners developed a strategy based on three elements: 1) Gather data from existing national and regional surveillance systems already involved in vaccine monitoring activities conducted by PHIs, 2) Leverage IVE capacity by supporting other PHIs willing to enhance vaccines monitoring in their region/country, 3) Build an agile network of hospitals/general practitioners' networks, through a yearly public call for sites-countries, with selection based on their experience/expertise in IVE studies and on DRIVE data needs.

More details on the strategy used by DRIVE to achieve a better stakeholder engagement (including National PHI) and communication is further developed in the DRIVE WP1 deliverable: D1.3 "Final report on governance and principles" section "Stakeholders' engagement and communication strategy".

Despite the notable PPP hesitancy perceived around many institutions in Europe, DRIVE efforts to engage with National PHIs as Associate Partners did not cease in the first four years of the project life. However, by the final year of DRIVE, the Coordination Team decided to put on hold its strategy for involving PHIs as they were dealing with the COVID-19 pandemic and subsequent immunization programs and therefore with little or no time to commit to DRIVE. Moreover, the low influenza circulation in the past two seasons and the existence of parallel and potentially overlapping European platforms (e.g. ECDC/EMA VEBIS,

IMOVE) raised several concerns on the added value of engaging PHIs in DRIVE's post-IMI future. Altogether, these factors have caused a stalemate in the DRIVE's network expansion.

Among the European National Public Health Institutes that DRIVE succeeded to on-board as Associate Partners are:

- Medical University Vienna (MUV, Austria): primary care setting, part of Diagnostic Influenza Network Austria, DINÖ).
- The Directorate of Health of Iceland (Embætti landlæknis, Iceland): mixed hospital and primary care setting.
- Laboratoire National de Santé (LNS) in Luxembourg: they participated in the 2018/19 and 2019/20 season, however they abandoned their status as Associate Partner, as could not commit to provide data to DRIVE in the context of the COVID-19 pandemic and also experienced hurdles with the ethics committee approvals.

Several others expressed interest yet postponed joining DRIVE, citing insufficient technical capacity or inconvenient timing due to COVID-19 crisis:

- Statens Serum Institute (Denmark)
- Sciensano (Belgium)
- Polish National Public Health Institute (Poland)
- Maltese Ministry of Health (Malta)

Other national PHIs told upfront they cannot participate in a public- private partnership because of the perception of being associated too closely with the industry.

3. Support to scientific coordination and ethical surveillance

During this period FISABIO in collaboration with SYNAPSE and SP continued with the coordination of the overall scientific aspects of the project facilitating the alignment of the developed activities with the achievement of the planned objectives and the proper interrelation among tasks of different WPs.

Regarding the ethical surveillance, FISABIO ensured compliance at all study sites. Approvals of the ethical committees of each site were required before the start of the studies (usually collected in September-October of the respective season). More details on the Ethics requirements per site are collected in D3.4.1 and D3.4.2 *Report on the comparison of adapted local protocols and Ethical Committee evaluation in each study site*. An **Informed Consent Form (ICF) template** was developed by FISABIO with the support from the WP1 members in June 2020. DRIVE ICF template aims to seek patient consent for secondary use of data and was developed jointly with the Open data strategy and secondary use of data framework. The ICF has been integrated in the latest DRIVE Generic TND protocol update (D7.1.3), which is now available for the DRIVE study sites (it is at their discretion whether to adapt this template, to use it as it is or to keep their own ICF).

4. Day to day management and communication

The Coordination Team met regularly, at least every two weeks, to discuss about the advance of the

project and solve any questions about scientific, technical and financial management. The Coordination Team offered continued support to DRIVE partners in the day-to-day management, especially in the following areas:

- Preparation and submission of the Grant Agreement amendments (changes in the members of the consortium, budget reallocation, inclusion of Third Parties, etc)
- Organization of Steering Committee meetings, including agenda preparation, escalation of internal issues.
- Organization of key project meetings, e.g. Annual Forum, General Assembly, Independent Scientific Committee.
- Resolution of questions about financial reporting and the eligibility of costs according to IMI rules.
- Monitoring of the writing review process and submission of deliverables.
- Establishment of internal procedures to assure the compliance of the DRIVE document review and site selection processes.
- Tracking work plan progress, milestones, review of risks and implementation of contingency plans when needed.

For the internal communication, the DRIVE mailing lists and SharePoint repository established in the first period and have been continuously updated in terms of contacts and access permissions by SYNAPSE. In this regard it is worth noting that a strict policy of access permissions is followed in the documents repository to prevent EFPIA partners from accessing WP7 documents, in line with DRIVE study independence from Vaccine companies. Additionally, new mail distribution lists were created as needed, for instance for the study sites (to keep a fluent communication among DRIVE WP7 partners and the sites), for the interactions with the QCAC, ISC, etc. Lastly, DRIVE newsletter is quarterly delivered to Consortium partners, Research Collaborators and external stakeholders, and the Coordination Team suggests topics for the newsletter to WP5. WP leaders schedule periodic meetings according to the project needs and Steering Committee are scheduled every two weeks by the Coordination Team.

5. Reporting and administration

FISABIO and SYNAPSE share the responsibility for producing the periodic report. For the financial part, SYNAPSE provided detailed guidance and instructions to partners of the basics about eligibility rules, categories of costs, reporting procedure, etc to ensure an appropriate reporting. An Excel template together with detailed instructions to enter the information in the system were developed to support those beneficiaries less familiarized with the Participant Portal. In addition, a calendar for the preparation of the financial report was also produced allowing two rounds of review of the reported figures by the Coordination Team.

For the scientific part, the coordinator FISABIO prepared the corresponding templates and coordinated the gathering of information and data from partners to produce the present report. FISABIO as project coordinator, is in charge of the submission of the periodic report to IMI. Once approved, FISABIO receives the funding corresponding to the accepted costs and manages its transfer to the rest of partners.

6. Contract and legal management

FISABIO has formalized the participation of the study sites (**Research Collaborators**) selected in the DRIVE Call for Tenders (4 editions: 2018/19, 2019/20, 2020/21 and 2021/22) through the signature of Research Collaboration Agreements (which include a detailed budget allocated to the particular study site). In terms of IMI rules, the new Research Collaborators act as FISABIO's Third Party Against Payment following Article 11 of DRIVE GA num. 777363 – Use of in-kind contributions provided by Third Parties against payment. The entities which have signed DRIVE RCA in the different call for tenders are included in Annex 1.

On the other hand, the contracting of **Associate Partners** that represent National Public Health Institutes and do not join through the Call for Tenders, has been done through an individual Associate Partner Agreements (APA). The entities which have signed DRIVE APA are included in Annex 1.

Finally, **Advisory Agreements** were also signed with the Independent Scientific Committee and Quality Control and Audit Committee members. These contracts were signed between FISABIO (as Project Coordinators and on behalf of the Consortium) and the advisors, who provided consultative and advisory services with no economic compensation for the performance of the services.

The Coordination Team has led the preparation and submission of two **amendments to the Grant Agreement**.

Changes included in AMD-777363-12 are listed in the following table:

Changes included	Topic
1	IRD termination. Effective end date: 18 July 2018 (As stated in IRD opinion letter)
2	INSERM as new partner (replacing IRD as leader of WP1)
3	OPGB as new partner (replacing ISS as leader of WP3). Start date: 1 September 2018
4	Medizinische Universität Wien (Austria) included as third party against payment under FISABIO (Article 11 of the GA)
5	Entities awarded in the Call for tenders (except DRIVE partners) participate as FISABIO's Third Party against payment (Article 11 of the GA). It is considered as a DRIVE service and included in the budget category "Other goods and services"
7	Update on deliverables and delivery dates; D6.1 removed, D2.6 removed, D3.5 delivery date changed from M14 to M26, D7.6, D7.7, D7.8, D7.9 delivery date changed
8	The following Deliverables were specified as "updated as needed": D1.1, D2.1, D2.4, D2.5, D3.1, D3.3, D3.4, D4.1, D4.3, D4.6, D5.4, D5.6, D5.8, D5.9, D7.1, D7.2, D7.3, D7.5
9	OPBG and INSERM roles explained
10	Reference to clinical studies and data collection
11	Remove references to mobile app
12	Addition of new deliverables related to the Annual Call for Tenders as per IMI officer´s request; D2.7. Report of the IVE Call for Tenders 2018; selection criteria, evaluation process and awarded studies (M23), D2.8. Report of the IVE Call for Tenders 2019; selection criteria, evaluation process and awarded studies (M28), D2.9. Report of the IVE Call for Tenders 2020; selection criteria, evaluation process and awarded studies (M40), D2.10. Report of the IVE Call for Tenders 2021; selection criteria, evaluation process and awarded studies (M52).
13	Reference to evaluation meeting in task 2.7
14	New Miriam Levi´s affiliation at Local Health Unit Tuscany Centre from the 3rd of October 2018 on as third party against payment
15	UNIFI Budget changes; (a) 30,000 € from subcontracting to personnel (24,000 € personnel + 6,000

Changes included	Topic
	€ OVH) and (b) 28,250 € moved from Other Direct Costs to personnel mainly to cover personnel costs provided by its third parties against payment Smallcodes, Plan Soft Local and the Health Unit Tuscany Centre
16	IRD budget reduction to the amount reported in the First Periodic Report
17	INSERM takes the rest of the budget of IRD and increases personnel category
18	ISS transfers part of its budget to OPBG
19	FISABIO transfers to SURREY the extra budget for the study (149.928,75 €, Call for Tenders 2018)
20	FISABIO transfers to OPBG the extra budget for the study (150.000,00 €, Call for Tenders 2018)
21	Caterina Rizzo is member of ISS until May 2018, from June 2018 she became part of OPBG research team
22	OPBG Partner description added
23	INSERM Partner description added
24	ISS Partner description review and include bio-sketch of the new team members
25	Efforts reallocation in all WP's
26	WP1 description changes: (i) Text added "*The WP leader will be IRD until M13, then FISABIO from M13 to M22 and INSERM from M23 to the end of the project. WP Co-Coordinator will be SP during the whole project. OPBG included from M15*", (ii) D1.2. Governance Standard Operating Procedures (SOP) changed from M3 to M5
27	WP2 description changes: (i) OPBG starts in M15, all previous tasks have been kept for ISS, (ii) Deliverables of the call for tenders have been included, (iii) In task 2.7 it has been added the following: *A yearly evaluation meeting will be organized with the awarded tender applicants. The outcomes of this meeting, selection criteria, evaluation process and awarded studies will be explained annually in deliverables D2.7, D2.8, D2.9 and D2.10 for seasons 2018, 2019, 2020 and 2021 respectively*, (iv) D2.6 has been removed as it was merged with D4.1 and submitted in M12
28	WP3 description changes: (i) INSERM was Included in Task 3.1, (ii) OPBG was included in Task 3.1 from M15, (iii) The text of Task 3.3 has been reviewed
29	WP4 description changes: (i) OPBG included in Tasks 4.1, 4.2 and 4.3 from M15
30	WP5 description changes: (i) In Task 5.1 the sentence "*This approach will be taken with other DRIVE communication tools, for example the Mobile App, where feasibility will first need to be established*" has been removed, (ii) OPBG was included from M15, (iii) Task 5.6 leadership transferred from IRD to UNIFI
31	WP6 description changes: (i) IRD participation period was included
32	WP7 description changes: (i) SURREY was included in Task 7.1.3, (ii) OPBG was included from M15, (iii) THL was added in Task 7.2, (iv) In the Description of work the following sentence was added "*In addition, we will execute the SWOT Plan developed in WP3 through direct interactions and discussion with the sites. The SWOT Plan will help to identify, for participating study sites, strengths, opportunities, limitations and gaps to conduct timely brand-specific vaccine effectiveness on a routine basis. The reports on the SWOT analysis will be generated from WP7 and also provided to the QCAC by WP7*", (v) In task 7.1.2 the following sentence was added "*In addition, we will perform the SWOT analysis to identify, for participating study sites, strengths, opportunities, limitations and gaps to conduct timely brand-specific vaccine effectiveness on a routine basis. These protocols will be modified, if necessary, based on the feedback of the SWOT report (deliverable 7.9)*". D7.10 lead was changed from OPBG to ISS.
34	Stefania Bellino and Ornella Punzo included as new team members of ISS
35	Changes in CoMO research team; Chris Head and Daphne Holt were removed, Nadia Vaenerberg and Elena Moya were included
36	UNIFI included two additional Third Parties; Plan Soft srl and Local Health Unit Tuscany Centre
37	Milestone 1 "Workshop open to external stakeholders to discuss the research agenda" date changed from M12 to M16
38	Milestone 4 "Complete the systematic review with recommendations for protocol development" date changed from M12 to M16
39	Milestone 12 name changed from "Methodology guidelines agreed and completed (first version)" to "Framework for analysis of influenza vaccine effectiveness studies agreed and completed (first version)" and date changed from M3 to M7
40	Milestone 19 "First communication plan agreed" date changed from M12 to M5
41	Milestone 22 "Study protocols accepted by the Independent Scientific Committee" date changed

Changes included	Topic
	from M7 to M3
42	Milestone 25 "Second seasonal final report on conducted studies completed" date changed from M22 to M25
43	Milestone 26 "Third seasonal final report on conducted studies completed" date changed from M34 to M36
44	Milestone 27 "Fourth seasonal final report on conducted studies completed" date changed from M46 to M48
45	Milestone 28 "Fifth seasonal final report on conducted studies completed" date changed from M58 to M60
46	New Milestone 29 "Evaluation meeting of the proposals received in the Call for Tenders 2019" included in M24
47	New Milestone 30 "Evaluation meeting of the proposals received in the Call for Tenders 2020" included in M36
48	New Milestone 31 "Evaluation meeting of the proposals received in the Call for Tenders 2021" included in M48
49	Deliverable D6.1 is removed as it was merged with D6.3 and submitted in M6
50	New Deliverable D7.10 "Written report on SWOT results" was included
51	INSERM added the Assistance Publique-Hôpitaux de Paris, AP-HP as Linked Third Party from 1/06/2019
52	Transfer of 3 PM from FISABIO to P95 in WP7 (19.500 €)
53	Six medical centres included as third party against payment under SURREY (Article 11 of the GA).
54	Budget transfer of 20,000 € (16.000 € Other Direct Costs and 4.000 € overhead) from FISABIO to IABS-EU budget

Changes included in AMD-777363-14 are listed in the following table:

Changes included	**Topic**
1	SURREY termination and transfer to UOXF
2	UOXF incorporation as new partner
3	Budget reallocation among partners; COMO, INSERM and FISABIO to P95
4	Budget reallocation among partners; FISABIO to P95 "Other Direct Costs" – processes audit and Open Access Fees
5	Budget reallocation among partners; FISABIO to INSERM – WP7 activities
6	Budget reallocation among partners; FISABIO to SURREY – WP7 activities
7	Budget reallocation among partners; SURREY to UOXF for activities transfer
8	FISABIO's Third Parties addition according to Article 11 of the GA (Use of in-kind contributions provided by third parties against payment
9	Efforts reviewed and updated by DRIVE partners
10	FISABIO's key personnel updated in Section 4.1 of Part B of Annex 1

7. Risk Management

To monitor the risks already foreseen in the DoA, assess their impact and detect new risks, the Coordination Team uses the risk register developed during the first year of the project. It follows a system of two variables (impact and probability) to evaluate the status of each risk. A three-point scale ranging from 1-Low to 3-High is used to score the impact and probability of the risk. The status for each risk is constructed by multiplying both variables. As a result, the state of the identified risks and the corresponding mitigation plan are monitored and reported in Annex 2 and in the IMI Participant Portal

(Critical Implementation risks and mitigation actions Section).

Sustainability Plan

The topic of DRIVE's project sustainability falls under the scope of DRIVE WP1 and it is further detailed in the deliverable D1.4 Generic post Authorization Development plan (in the format of a white paper). The white paper provides critical information on DRIVE's sustainability (platform, possibility of network evolution, regulatory aspects, costs and funding mechanisms) and inform on European possibilities for monitoring effectiveness for the next generation of influenza vaccines and other respiratory diseases vaccines including COVID-19.

In general terms, the sustainability post-IMI of the DRIVE platform will be ensured by two main pathways:

- Under DRIVE partners' remit:
    - Leverage of the DRIVE Open data research and secondary use framework by sustaining DRIVE's database (data collected by DRIVE from 2017/18 to 2021/22), coordinated by FISABIO and P95.
    - Maintenance of the DRIVE website over the project end, responsibility of UNIFI and FISABIO.
    - A legal framework provided by a Memorandum of Understanding (MoU) among DRIVE Consortium partners interested in continuing the collaboration. The DRIVE MoU will promote the sustainability of the DRIVE community and to continue engaging dialogue with EU institutions. It will allow the sustainability of the DRIVE database and website, ensuring that the remaining DRIVE funds will be provided by EFPIA for this purpose. The MoU is currently under development by the DRIVE Coordination Team (see specific section below).
- Use of the DRIVE platform assets (e.g. IT infrastructure, study site network) and lessons learnt by DRIVE partners in building the COVIDRIVE consortium (see section on COVIDRIVE).

The present deliverable provides an operational oriented view on how DRIVE intends to partially sustain its activities beyond the IMI umbrella that complements the information detailed in DRIVE WP1 deliverable "Real-World Evidence infrastructure for vaccine monitoring in Europe. From proof of concept to sustainability".

DRIVE website, social media and document repository maintenance

The DRIVE website (https://www.drive-eu.org/) is currently maintained and managed by UNIFI and the domain is hosted by SYNAPSE. After the project end in June 2022, the DRIVE website will be preserved **for at least 1 year** (with option to extend additional years)**,** with three main objectives:

- As a repository to store and make available all DRIVE public deliverables and scientific outputs.
- As a focal point to disseminate key achievements of the post-IMI DRIVE, including relevant publications associated with the project.
- As a point of information about DRIVE Open data and secondary use framework and as a platform to receive and coordinate potential Additional Analysis Requests.

The **post-IMI management and maintenance of the DRIVE website** will be **responsibility of UNIFI**. The website will be streamlined and only the project's basic information will be kept. Moreover, an ad-hoc section for the Open data and secondary use requests will be implemented. More details on the DRIVE website maintenance (characteristics and costing) can be found in the UNIFI-Dynamedics proposal post-DRIVE (see Annex 3). The website domain will be transferred from SYNAPSE to FISABIO. This minor cost will be reported by FISABIO under Periodic Report 5, and will allow the maintenance of the DRIVE website domain until 4th of July 2023.

The activities performed by UNIFI after the DRIVE project end (30th of June 2022), will be funded by EFPIA (using the remaining funds of DRIVE) and will be regulated by DRIVE MoU, respecting the UNIFI/Dynamedics proposal (see Annex 3) approved by the Steering Committee.

DRIVE Social media profiles (Twitter and Linkedin), currently managed by UNIFI, will be **transferred to FISABIO**, which will only sporadically post updates on key publications, events or actions linked to the post-IMI phase of DRIVE.

Finally, DRIVE will stop using Microsoft SharePoint as the **project document repository** (currently managed by SYNAPSE). After 30th June 2022, all the key project documents and materials (deliverables, minutes, meeting materials, administrative documents) will be **stored in a private FISABIO cloud server** (HERMES and the Vaccine Research Department central storage server) and local copy of the whole DRIVE SharePoint will also be stored at FISABIO facilities. In the post-IMI era of DRIVE, the documents will be accessible to all the partners upon request to FISABIO. The WP leaders have been responsible of selecting the key documents and materials to be stored in FISABIO cloud for each of the DRIVE WP. All public deliverables and study documents will also be stored and available in the DRIVE website, for at least 5 years.

DRIVE database maintenance

The **maintenance and management of the DRIVE database** will be **responsibility of P95**, for a duration of at least 1 year (with option to extend additional years). More details on the DRIVE database maintenance (characteristics and costing) can be found in the P95 proposal post-DRIVE (see Annex 4). The activities performed by P95 after the DRIVE project end (30th of June 2022), will be funded by EFPIA (using the remaining funds of DRIVE) and regulated by DRIVE MoU, respecting the P95 proposal (see Annex 4) approved by the Steering Committee.

DRIVE Open data research framework for secondary use of data

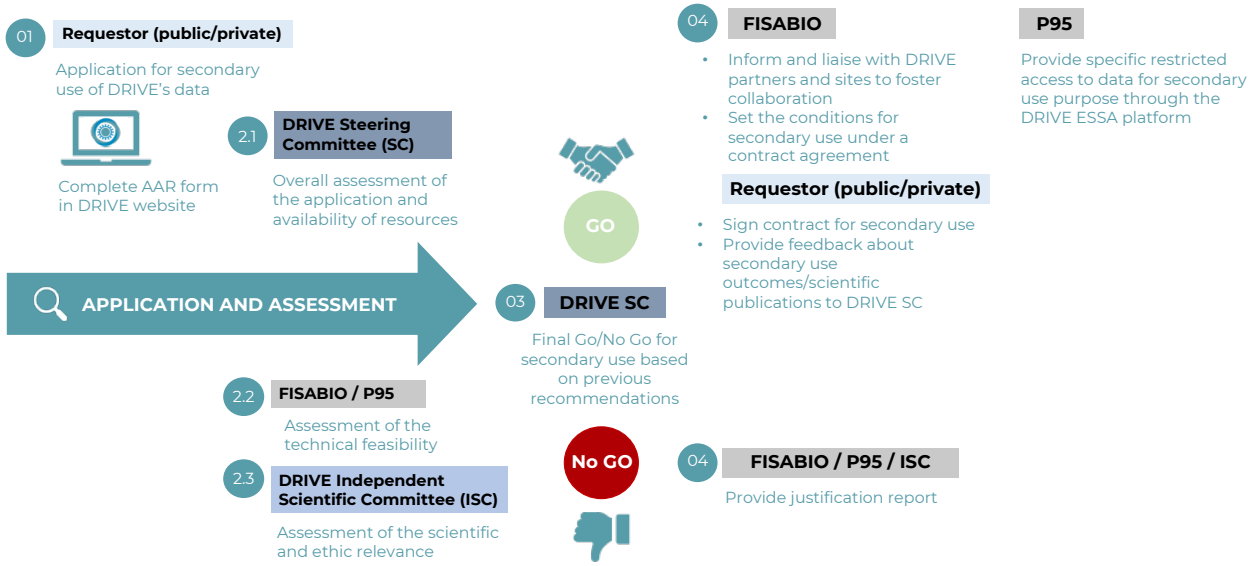
DRIVE WP1has developed a framework of the open data strategy and secondary use of data to value DRIVE dataset (built along the 5 influenza seasons) and advanced knowledge in IVE and beyond, which represents a key component for the platform sustainability. More details of the DRIVE Open data research proposal can be found as Annex 9 of the DRIVE WP1 deliverable.

DRIVE partners initially developed this proposal at the end of 2020 and during the final year of the project (Q2 of 2022) launched the open access for research data framework, which will be posted in the DRIVE website.

Several internal processes have been put in place to receive, assess, coordinate and track the potential Additional Analysis Requests (AAR) to use DRIVE data for secondary purposes. DRIVE Open data research proposal can be found as Annex 9 of the DRIVE WP1 deliverable D1.3 *"Final report on governance and principles"*.

The activities performed by P95 and FISABIO after the DRIVE project end (30th of June 2022), will be regulated by DRIVE MoU. Moreover, a collaborative agreement will be signed by P95 and FISABIO to regulate the management of the AAR.

Figure 5: Process for assessing DRIVE Additional Analysis Requests, coordinated by FISABIO and P95.



In summary, any former DRIVE Consortium Partners, Research Collaborators or Associate Partners; or Third Parties (Requestor/Applicant), will be able to make an application for secondary use of DRIVE dataset by completing an Additional Analysis Request form which is available on the DRIVE website.

DRIVE WP1 and WP5, with the Coordination Team supervision, will develop a specific website section that will contain the detailed Open data research proposal, a summary of the proposal in the format of Frequently Asked Questions, a "patient information corner" and the Additional Analysis Request (AAR) form, for Requestors/Applicants to complete and submit. This website section ensures proper information and transparency of secondary use project on DRIVE website.

The coordination and management of the AAR will be managed by FISABIO/95 and the costs associated to the coordination and data extraction activities will be paid by the Requestor to FISABIO and P95 directly under a specific legal agreement (minimum pre-defined fees to be defined, but non for profit). FISABIO/P95 will seek several recommendations before providing the green light to the Requestor:

- P95/FISABIO will perform an assessment of the technical feasibility of the secondary use
- DRIVE Independent Scientific Committee will assess the scientific and ethical relevance of the secondary use.
- Finally, the Steering Committee will perform an assessment in terms of intended use and required privacy authorisation.

The final approval will be provided by the Steering Committee, based on the abovementioned assessments. Once approved, FISABIO will execute the administrative arrangements with the Requestor

(under a specific agreement to be defined, including the proposed budget for Request coordination) and P95 will support the secondary data analysis and/or provide specific restricted access to data for secondary use of the Requestor, through the DRIVE Electronic study support (web) application platform (ESSA). Finally, the Requestor will acknowledge DRIVE in the publications derived from the secondary use of data and provide feedback about the outcomes/scientific publication to Steering Committee.

Post-IMI DRIVE legal framework: Memorandum of Understanding

DRIVE partners propose a Memorandum of Understanding (MoU) among DRIVE partners for post-IMI activities. The DRIVE MoU is currently under development by the DRIVE Coordination Team and will allow to:

- Ensure the governance of DRIVE post-IMI Open data and Secondary use framework, as well as to coordinate and assess any potential Additional Analysis Requests.
- Organize periodic meetings to maintain a constant dialogue among the participating DRIVE partners. FISABIO would organise DRIVE SC touch points every 3 months for coming 3 years. This mechanism will allow to maintain dialog between public and private partners and European institutions about the future and value of PPP in vaccines monitoring.
- Ensure that the remaining DRIVE funds will be used for DRIVE database and website maintenance over the IMI project end (30 June 2022). The MoU will specify that DRIVE Database and website maintenance (for at least one year) will be funded by EFPIA partners with the DRIVE remaining budget in Q1 2023.

COVIDRIVE: beyond a proof of concept of DRIVE

Besides influenza vaccines, no other vaccines are being evaluated in DRIVE. However, the emergence of COVID-19 and the unprecedent push in vaccines investment, highlighted the value of rapidly setting up a public-private platform to assess brand specific COVID-19 vaccine effectiveness. Furthermore, the use of existing/established EU efforts to assess COVID-19 vaccines in real-life settings was recommended by the EMA as part of the core requirements in the Risk Management Plan for COVID-19 vaccines.

DRIVE has demonstrated the added value of joint public-private European platforms and their potential to be applied to other vaccines post-marketing evaluation, having as a clear use case the setup of COVIDRIVE, for COVID-19 vaccines effectiveness monitoring. In November 2020 several DRIVE partners (namely FISABIO, P95, THL, Sanofi and GSK) initiated **COVIDRIVE** (http://covidrive.eu/)**,** which has gradually expanded and is now a consortium composed of 11 partners (Figure 6).

Figure 6. COVIDRIVE consortium partners. 3 non-industry partners and 8 vaccine companies are part of COVIDRIVE, as of April 2022.

Two members of the DRIVE Coordination Team (FISABIO and Sanofi) played a key role in the genesis and development of the COVIDRIVE platform. Furthermore, FISABIO and P95, both DRIVE partners, are the Co-Coordinators of the COVIDRIVE consortium and related studies. More information about COVIDRIVE can be found in the COVIDRIVE Governance charter (COVIDRIVE Governance Charter v5.3)

DRIVE lessons learnt were cardinal for the rapid setup of COVIDRIVE (Study network, Vaccine effectiveness methods, study platform governance, IT infrastructure for data collection and pooled analysis). COVIDRIVE proposal was endorsed by EMA in December 2020 and then proposed to COVID-19 Marketing authorisations holders at a Vaccines Europe meeting (Task Force for COVID-19 vaccines, epidemiology and pharmacovigilance). The COVIDRIVE consortium agreement was signed in June 2021 (COVIDRIVE launch press release) and the study platform is started its first COVID-19 vaccine effectiveness study in September 2021 with the inclusion of the first patient in Valencia (Spain) (COVIDRIVE study kick-off press release).

DRIVE has gone beyond the proof of concept with the creation and establishment of COVIDRIVE as a European platform for COVID-19 vaccines effectiveness monitoring, and potentially for other vaccines (RSV, influenza…) in the near future. However, the added value of such PPP universal platform for vaccines post-authorisation studies is still in question. The recent changes in the vaccines monitoring environment with the joint EMA/ECDC platform and the related ECDC call have raised multiple pragmatic considerations and questions the feasibility and need to sustain the DRIVE study platform.

At a meeting organized by Vaccine Europe in March 2021 with COVIDRIVE /EMA/ECDC, ECDC explained that they cannot “share” sites/subjects with COVIDRIVE initiative to secure independence of the studies, meaning that sites co-funding cannot be considered. This constitutes an important hurdle that deserves further discussion. Indeed, competitions for sites between the various initiatives will be detrimental for all; in some countries, only few sites are able to perform CVE studies so the question is how this can be managed. Considering the above, the COVIDRIVE and DRIVE consortiums will engage a dialogue with EMA and the European Commission, with the support of Vaccines Europe, to discuss pragmatically the requirements, the feasibility components and the rationale and value to sustain the public-private platforms for vaccines effectiveness monitoring in the coming years.

Conclusion

The present deliverable summarizes the project key achievements, lessons learned, challenges and improvements made, with a focus on the leading role of WP6 in the management and coordination of the project. Since its launch in 2017, DRIVE project:

- tested a PPP governance model that can be adapted and adjusted for other public-private collaborations;
- performed IVE studies for 5 consecutive years, despite the challenges posed by the COVID-19 pandemic and the hesitancy around the PPP;
- allowed vaccine manufacturers to answer to regulatory commitments;
- built a ready-to-use IT infrastructure and study site network;
- gone beyond the proof of concept and tested the feasibility of its PPP model to address the COVID-19 pandemic with the genesis of COVIDRIVE;
- engaged high-level discussions with EU institutions about the future of PPP in generating Real World Evidence

Several operational aspects of DRIVE's sustainability post-IMI are also described in this report, including the plan for DRIVE website, social media and document repository maintenance, the DRIVE database maintenance and the DRIVE Open data research framework for secondary use of data.

Finally, we report on a vital part of DRIVE's sustainability, the COVIDRIVE project. COVIDRIVE's long term vision of becoming a universal platform for VE monitoring of vaccines and treatments effectiveness for several infectious respiratory diseases (COVID-19, influenza, RSV…) will be one legacy of the DRIVE project.

Annex 1: Summary of the entities signing DRIVE Research Collaborator or DRIVE Associate Partner Agreements.

Num.	Entity	Country	Influenza Season	RoI
1	Medizinische Universität Wien	Austria	2017/2018	Associate Partner
8	Medizinische Universität Wien	Austria	2018/2019	Associate Partner
9	Laboratoire National de Santé	Luxembourg	2018/2019	Associate Partner
2	Vall d'Hebron University Hospital	Spain	2018/2019	Research Collaborator
3	CIRI-IT (test negative design)	Italy	2018/2019	Research Collaborator
4	CIRI-IT (cohort study)	Italy	2018/2019	Research Collaborator
5	Helsinki University Central Hospital	Finland	2018/2019	Research Collaborator
6	Kapodistrian University of Athens Medical school	Greece	2018/2019	Research Collaborator
7	National institute for infectious Diseases (Matei Bals)	Romania	2018/2019	Research Collaborator
10	Medizinische Universität Wien	Austria	2019/2020	Associate Partner
13	Helsinki University Hospital	Finland	2019/2020	Research Collaborator
11	Interuniversity Research Centre on Influenza and other Transmissible Infections, CIRI-IT - Primary Care TND	Italy	2019/2020	Research Collaborator
12	Interuniversity Research Centre on Influenza and other Transmissible Infections, CIRI-IT - Hospital TND	Italy	2019/2020	Research Collaborator
14	Hospital Universitario La Paz/ IdiPAZ	Spain	2019/2020	Research Collaborator
15	Hospital Universitario Vall d'Hebron	Spain	2019/2020	Research Collaborator
16	Hospital Universitario Germans Trias i Pujol	Spain	2019/2020	Research Collaborator
17	National Institute for Infectious Diseases	Romania	2019/2020	Research Collaborator
18	Medizinische Universität Wien (MEDUNI WIEN)	Austria	2020/2021	Associate Partner
19	Iceland Directorate of Health	Iceland	2020/2021	Associate Partner
20	Hospital Universitario Vall d'Hebron	Spain	2020/2021	Research Collaborator
21	Interuniversity Research Centre on Influenza and other Transmissible Infections, CIRI-IT, BIVE Network	Italy	2020/2021	Research Collaborator
22	Hospital Universitario La Paz	Spain	2020/2021	Research Collaborator
23	Hospital Rey Juan Carlos	Spain	2020/2021	Research Collaborator

24	Hospital Universitario de Salamanca	Spain	2020/2021	Research Collaborator
25	National institute for infectious Diseases (Matei Bals)	Romania	2020/2021	Research Collaborator
26	Hospital Universitario Germans Trias i Pujol	Spain	2020/2021	Research Collaborator
27	Medizinische Universität Wien	Austria	2021/2022	Associate Partner
28	Iceland Directorate of Health	Iceland	2021/2022	Associate Partner
20	Hospital Universitario La Paz	Spain	2021/2022	Research Collaborator
21	Hospital Universitario Germans Trias i Pujol	Spain	2021/2022	Research Collaborator
22	Hospital Universitario Vall d'Hebron	Spain	2021/2022	Research Collaborator
23	Hospital Universitario de Salamanca	Spain	2021/2022	Research Collaborator
25	Interuniversity Research Centre on Influenza and other Transmissible Infections, CIRI-IT, BIVE Network	Italy	2021/2022	Research Collaborator
26	National institute for infectious Diseases (Matei Bals)	Italy	2021/2022	Research Collaborator

Annex 2: DRIVE Risk identification and mitigation plan tracker.

Risk Register

Risk ID number	Open/ Closed	Character	Risk Description	Mitigation Plan	Specific measures	Status	Date Identified	WP related	Owner	Risk Treatment	Target Resolution Date	Proximity	Impact	Probability	Status2	Notes / Updates
1	Open	Political	Limited participation of PHIs. The fact that ECDC and national public health institutes were not able to join during Stage 2 was considered to translate into an increased risk of failure to meet the objectives of the call topic by the reviewers at FP evaluation stage. Therefore, a review at M24 was proposed by the consortium and endorsed by the reviewers during the Stage 2 evaluation to mark a go/no go decision point. If criteria put foward by reviewers and listed in the DoA are not met by the time of the M24 review, IMI may consider to terminate the project.	Increase the number of academia centers or other networks collecting data. Increase intensity of the public sector engagement approach (more face to face meetings and negotiations).	As lack of collaboration of PHIs with DRIVE is due to perception, DRIVE is exploring the possibility of encouraging open data.	Discussion with PHIs continue, Luxembourg came on board for 2018-19 season. Discussion with ECDC about the future of open data, TESSI, etc.	Stated in the DoA	WP7	WP7 & SC	Avoidance	two years of the project	Medium (3-12m)	3	2	6	
2	Open	Technical	Short time to perform the first study in 2017	Tools and protocols to be initiated by Mid-June even if the official start of the project is expected in July, the 1st.	Preparing the protocols for review in early 2018 will facilitate their adoption, review process and approval by ethics committee for next season. For these reasons, D7.1 and D7.2 have been officially delayed from M3 to M7.	(D7.1 and) D7.2 under review	Stated in the DoA	WP1, WP2, WP3, WP4, WP5, WP6, WP7	WP7	Avoidance	first semester of the project	Short (<3m)	2	1	2	
3	Open	Technical	Issues with validation through vaccine registry data, medical record reviews or other documentation	Sensitivity analysis performed to assess the risk of bias.	As this is a sensitive topic, different approaches are being analyzed. For the pilot season no sensitivity analysis was performed	D2.4 under review	Stated in the DoA	WP2, WP3, WP4, WP7	WP2	Avoidance	first semester of the project	Medium (3-12m)	2	1	2	
4	Open	Technical	Effective communication and coordination across work packages may be suboptimal	Proactively develop policies and procedures which encourage transparency and coordinated activities.	Regular TCs between Fisabio and each WP continue. To ensure effective communication across work packages, an update of the WPs work done takes place once a month during the Steering Committee meeting.	No problem has been seen, so far	Stated in the DoA	WP1, WP2, WP3, WP4, WP5, WP6, WP7	CT	Mitigation	first semester of the project	Medium (3-12m)	3	1	3	
5	Open	Technical	Effective gathering, cleaning and integrating databases may be suboptimal	A standard system will be adopted at the initiation of the project which has the capability to address all data storage and integration requirements.	The ESSA is set on place, and working smoothly. Good communication between FISABIO, P95 with all the study sites.	ESSA on place	Stated in the DoA	WP2, WP4	WP4	Mitigation	fisrt year of the project	Medium (3-12m)	3	1	3	
6	Open	Political	Data governance and ethical approvals are not obtained in time	Approvals to be initiated by Mid-June even if the official start of the project is expected in July, the 1st.	Ethical approvals for the sites sharing data are requested in the agreement.	Ethicals approvals received on time.	Stated in the DoA	WP7	WP7	Avoidance	fisrt and 2nd year of the project	Long (>12m)	3	1	3	
7	Open	Technical	Insufficient sample size	Additional study sites will be added, increasing the number of study tenders.	Annual tenders for new sites. Approaches, face to face meetings with different PHIs. Invitation of all PHIs to the annual meeting to take place in July 2019	Good acceptance of the 2019 tender, with over 13 new study sites /networks providing data for the 2019-20 season	Stated in the DoA	WP2, WP6, WP7	WP7	Avoidance	first year of the project	Long (>12m)	3	2	6	
8	Open	Technical	Insufficient quality standards reached or non-compliance identified	Exclusion criteria applied and sensitivity analysis performed to assess the impact of low quality.	Contracting a CRO envisaged to ensure a correct level of confidence on data collection.	QCAC advising on quality needs. P95 performing quality assessment of the data.	Stated in the DoA	WP1, WP2, WP3, WP4, WP5, WP6, WP7	SC	Mitigation	first year of the project	Long (>12m)	2	1	2	
U1	Open	Technical	Communication with EMA may be suboptimal	IABS-EU has the expertise to provide internal advice from a regulatory perspective to the consortium and to interact informally with EMA. Moreover, a regulatory group will be set-up in order to keep all partners informed about the regulatory requirements and to discuss in an effective manner the final messages/questions to be delivered to EMA	Contact with the Vaccine Working Party of EMA, through a Teleconference. Also attended the Annual Forum and were speakers in a workshop.	Regulatory group already set-up and purprose of the group being formally written.	December 2018	WP5	SC	Mitigation	first year of the project	Long (>12m)	2	2	4	
U2	Open	Political	Anti-vaccine groups / Anti-industry activists	Media monitoring team to flag any attacks		No problem has been seen, so far		WP5	WP5	Mitigation	first year of the project	Long (>12m)	3	1	3	
U3	Open	Political	A respected authority (scientist, university professor, specialist doctor in flu) with opposing views	Prepare standby statements – Q&A and graphics Select and train DRIVE spokesperson/interviewees (Maybe via video conference).				All	SC	Mitigation	first year of the project	Long (>12m)	2	2	4	
U4	Open	Political	Countries outside the core 7 with a completely different view of flu vaccines	Specific countries will have spokespersons fluent in local language for the interviews				All	SC	Mitigation	first year of the project	Long (>12m)	3	2	6	
U5	Open	Political	Governments with suspicions about credibility of the network	Lobbying team (if any) on standby to let the opposing countries/governments "see the light"				All	SC	Mitigation	first year of the project	Long (>12m)	3	2	6	
U6	Open	Political	Limited proposals received in the call for tenders launched on the 25/05/2018	To further disseminate the call for tenders through partner´s social media and personal contacts	To extend 10 days the deadline	We received enough tenders to increase the sample size		WP2	SC	Mitigation	first year of the project		3	1	3	

Annex 3: UNIFI proposal for post-IMI maintenance of DRIVE website.

Annex 4: P95 proposal for post-IMI maintenance of DRIVE database