D6.4 Project Assessment

777363 - DRIVE

Development of robust and innovative vaccine effectiveness

WP6 – Project management, coordination and sustainability

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List of abbreviations

ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EU	European Union
IMI	Innovative Medicines Initiative
ISC	Independent Scientific Committee
IVE	Influenza Vaccine Effectiveness
KPI	Key Performance Indicators
MHA	Marketing Authorisation Holders
NCA	National Competent Authority
PHI	Public Health Institute
PPP	Public Private Partnership
SC	Steering Commitee
VWP	Vaccines Working Party
WP	Work Package

Publishable Summary

The present document aims at reporting the interim evaluation conducted by the consortium in order to assess the degree of fulfilment of the project's objectives and KPIs. Conclusions of the assessment, along with the IMI reviewers' report following the DRIVE mid-term review undertaken in September 2019, will allow for the prompt detection of potential deviations in the work plan and the corresponding development of corrective measures to attain the objectives of the project in the most timely and efficient manner.

Introduction

There is an increasing demand from politicians and public alike to demonstrate the impact of the public health interventions put in place, seasonal influenza vaccination programmes included. The single most important challenge in achieving IVE studies for the various influenza vaccines put every year on the European market is the ability of the different stakeholders to work in collaboration, and here is where the DRIVE project comes in, with the crucial objective of developing a sustainable platform for IVE evaluation formed by both public and private entities.

A second challenge for DRIVE is to reach the capacity to perform brand specific vaccine effectiveness assessment on an annual basis. That requires a platform that is flexible enough to deliver the needed outputs in timely manner, robust enough to ultimately be able to generate results according to more granular specificities such as age, risk conditions, etc. flexible enough to utilize novel tools and become self-sustainable.

The DRIVE consortium engages into continuous dialogue with ECDC to define an acceptable governance model that would satisfy the PHIs requirements regarding the role of EFPIA, but also remain aligned with the spirit of a PPP. Those discussions led to the development of a governance model covering both the project and the annual IVE studies, yet given the political challenge in Europe around the involvement of vaccine manufacturers in activities that are usually and historically carried out by public health research groups., Given the unique framework proposed by DRIVE and the public private partnership approach toward a common goal, it has been it has been extremely difficult for many PHIs to commit to join the DRIVE project upfront.

In the present report, the consortium will assess the degree of fulfilment of the project's objectives and KPIs, with a particular focus on the main challenges above described. Conclusions of the assessment, along with the IMI reviewers' report following the DRIVE mid-term review undertaken in September 2019, will allow for the prompt detection of potential deviations in the work plan and the corresponding development of corrective measures to attain the objectives of the project in the most timely and efficient manner.

DRIVE key performance indicators

At the beginning of the project, there was considerable uncertainty about the success of the proposed PPP strategy for DRIVE, and for this reason the consortium agreed to conducting a technical audit based on the following key performance indicators (KPI) that were endorsed by IMI experts:

1. Success in **including additional national or regional Public Health Institutes**, preferably including at least one country that has not previously structurally estimated influenza vaccine effectiveness. This should include an increase in NPHIs as data providers, but also as affiliated partners (called 'Associate Partners' in the project), or as members of the Independent Scientific Committee (ISC).
2. Interpretable **vaccine effectiveness estimates** for more than one vaccine brand and in more than one risk group, including data from at least one country that has not previously structurally estimated influenza vaccine effectiveness (i.e. who have not sustainably contributed data year-in year-out to estimate IVE in Europe).
3. The successful piloting of a detailed **approach to select sites** according to brand distribution and appropriate sample size.
4. A metric on the success and **acceptability of the governance model**, possibly including qualitative data from current partners and other future stakeholders/partners.

The status of the KPIs after two years and a half of project implementation is described below:

1. Including additional Public Health Institutes

The strategy to increase the number of PHIs participating in DRIVE consisted in involving PHIs & research bodies in the IVE studies and scientific discussions; and reaching out to public organizations who have existing IVE studies who could join DRIVE as Associate Partners or as data providers.

In season 2018/2019 two PHIs were included (Luxembourg, which had not previously structurally estimated influenza vaccine effectiveness, and Romania) and in season 2019/2020, one additional PHI was included

(Denmark). On top of that, INSERM (France) agreed to join DRIVE and was formally proposed to be incorporated as a consortium partner 2019 (amendment submitted to IMI in July 2019).

Moreover, with the purpose of including additional national or regional PHIs several face-to-face meetings are currently being organized with key PHI and institutions. DRIVE established a ranking considering the countries that are not yet represented in the network having existing surveillance systems in place and their influenza vaccination coverage (focusing on vaccine coverage over 40%), and subsequently, the consortium is currently working on organizing meetings with the PHIs of countries in the top ten positions (UK, Netherlands, Belgium, Spain, Portugal, Ireland, France, Sweden, Germany and Malta). The first face to face meeting took place on November 25 in Brussels with Sciensano, the Belgian institute for health and a second teleconference meeting was held on November 26 with Germany's Public Health institute RKI. The meetings will be prepared thoroughly, defining clear objectives per institution and adapting questions/topics for discussion accordingly (including also research topics) to ensure PHIs see the value of contributing to DRIVE.

2. Vaccine effectiveness estimates

In season 2018/2019, interpretable IVE was generated from the Finnish register-based cohort for 2 brands in 2 targeted populations for vaccination: children and elderly. The register-based cohort however did not include data from countries that had not previously structurally estimated influenza vaccine effectiveness, as required by the KPI definition.

Data on the published tenders regarding influenza vaccine procurement were used to support the 2019-20 site selection taking into account brand/type availability, which was good, yet we learnt that public data is insufficiently informative to determine brand availability in advance of the season and requires substantial efforts to collect. In fact, recent licensures of new vaccines limit the value of historic tender data to predict brand or type availability at present.

A prospective mechanism of site selection based on expected vaccine brand availability is currently limited in its applicability due to a broad sample size gap, but some opportunity exists to prospectively target sites on the basis of vaccine type. This does depend on how vaccine recommendations and procurement systems evolve. Seasonal influenza vaccines are primarily licensed via Mutual Recognition Procedure (MRP)/decentralised procedures and thus supervising, National Competent Authorities (NCA) are Germany, Italy and The Netherlands. Marketing Authorisation Holders (MAH) have the obligation to submit Brand specific data to the NCA, via Type II Variation for "local" evaluation and approval, but the process entails some potential challenges, e.g. different interpretation of the data by different NCA, discrepancies on what to conclude, etc.

DRIVE consortium has had an ongoing interaction with EMA since the beginning of the project. EMA is willing to coordinate a harmonized evaluation of DRIVE report, and the Vaccine Working Party (VWP) will become involved before submission of brand specific data to NCA. In addition, the DRIVE annual report results will be discussed with the VWP. These efforts will facilitate the evaluation that will start at the NCA's after submission of the brand specific data.

In December 2018 a meeting took place between DRIVE and VWP which led to the recommendation to not submit the Type II variation as the pilot results were inconclusive. This year we have a comparable scenario, the DRIVE annual report has been submitted to EMA who will distribute it to VWP. Submission of brand specific Type II variation thereafter by the MAH.

As an additional regulatory initiative, for season 2020-21 and 2021-22 more interaction with EMA/VWP is planned. Indeed, if possible, a F2F workshop will be organized in Q2 2020 to better align the wishes and sighing's of the regulators.

The challenges faced by DRIVE to on-board PHI and/or access their data were discussed with VWP a year ago. VWP is well aware of the difficulty, yet it cannot help DRIVE to solve this issue. DRIVE would like to have feedback from VWP on the project methodology (e.g. adjustments to the protocols) and EMA agreed that the biostatistical group from EMA takes part in discussions on the methodology.

3. Sites selection approach

DRIVE developed a detailed process for site selection to expand the study platform network of research collaborators, which was not focused on brand specifically because the primary need at this stage is to expand the network and enlarge the number of sites contributing.
. Data on the published tenders and from the site proposal were available to support the 2019-20 sites selection taking into account brand/type availability (although it was not a key criterion).

The first Call for Tenders to cover IVE studies in the 2018/19 influenza season was launched in May 2018. The 12 proposals received were scored by DRIVE Steering Committee using the pre-defined criteria. After the SC evaluation, 8 sites were selected to be included in DRIVE IVE studies for season 2018/19 (Figure 1).

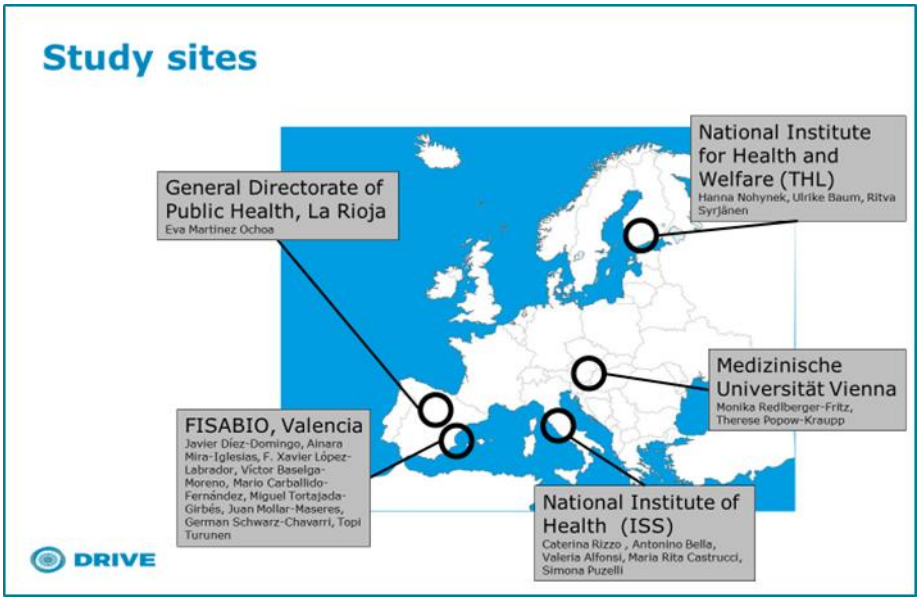

Figure 1. Selected sites for IVE studies (season 2018/2019)

The Call for tender and site selection process was refined and improved the subsequent season.
To recruit research collaborators to conduct to conduct IVE studies for 2019/20 influenza season, call for tenders were launched in early February 2019 allowing enough time for sites to apply and for DRIVE to assess the proposals with the final decision made in July 2019. Learning from the previous season also allowed to further define the priorities, in terms of potential new countries, target population vs general population, and to better evaluate the cost-effectiveness component. On this occasion, the Independent Scientific Committee (ISC) was also involved in the evaluation of the proposals submitted to the call, and the evaluation process was split in two phases: On one hand, the ISC provided a quantitative scoring of the proposals' scientific aspects (Table 1) and on the other hand the SC performed a qualitative assessment of the proposals' applicability and sustainability in DRIVE (Table 2). A total of 15 applications were received. After the two-step evaluation process, 6 proposals were rejected and 9 selected to be included in DRIVE IVE studies for season 2019/20 (Figure 2).

Topics / criteria		Max. number of points	Comments and references
Choose one	a) Ability to adhere to DRIVE protocols (conventional study design: TND, cohort)	15	*partial compliance (e.g. TND using local protocol) around 7 p.* *full compliance (e.g. TND study inspired by DRIVE protocol) around 15 p.*
	b) Level of appropriateness for DRIVE (innovative study design)		*referring to call text*
Ability to capture brand-specific information		10	*no brand information 0 p.* *info by patient recall around 5 p.* *complete info from EMR or vaccine registry around 10 p.*
Estimated sample size (in terms of LCI for convientional designs and ILI for innovative designs)		10	*<30 LCI /ILI- 0 p.* *30-100 LCI/ILI - around 4 p.* *100-500 LCI/ILI - around 8 p.* *>500 LCI/ILI - around 10 p.*
Scientific reliability of the laboratory testing or ability to send samples for DRIVE testing		10	*antigen tests only, or no laboratory confirmation and no ability to send samples 0 p.* *RT-PCR - virus type (A vs. B) or ability to send samples for DRIVE testing 5 p.* *RT-PCR - subtype/lineage 8 p.* *RT-PCR + capacity to NGS 10 p.*
Expertise in conducting influenza vaccine effectiveness		5	*demonstrated by publications or other references*
Total		50	

Table 1. Structure of the quantitative scoring of the proposals' scientific aspects performed by ISC

Topics / criteria	Comments and references	Assessment
ISC scientific evaluation and recommendation	refer to ISC evaluation	quantitative scoring per proposal (/50 poins)
Ability to fill gaps and relevance for pooled analysis in DRIVE	refer to gaps tables per vaccine type/brand by age (children, adult, elderly) and setting (hospital, GP)	Pooling not possible Pooling possible → Gaps filled → LCI>100 Gaps filled → LCI<100 Gaps not filled → LCI>100 Gaps not filled → LCI<100
New partner	PHI, organisation or country	New PHI New country and/or new organisation Other
Cost-effectiveness / co-funding / sustainability	refer to benchmark analysis + % of co funding	Budget requested < DRIVE benchmark Budget requested ≤ DRIVE benchmark + 25% Budget requested > DRIVE benchmark + 25% co-funding < 30% ★ 30% ≤ co-funding < 60% ★★ Co-funding ≥ 60% ★★★

Table 2. Structure of the qualitative assessment of the proposals' applicability and sustainability in DRIVE

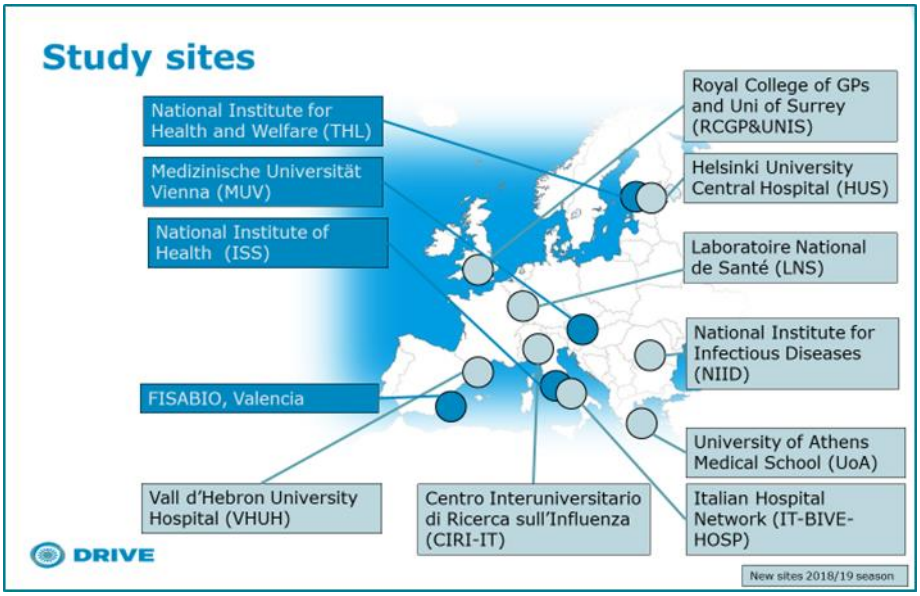

Figure 2. Selected sites for IVE studies (season 2019/2020)

4. Acceptability of the governance for the Study Platform

Governance model proposed

To develop the DRIVE Study Platform (shown below in Figure 3) the consortium followed guidance obtained from IMI PPP structure, ADVANCE Guidance for vaccine post marketing settings as well as the 2 years discussion with ECDC for their participation. All details of the governance structure of the Study Platform are included in the deliverable 1.5, which gives an overview of the governance to date and provides an insight into the adaptations made following feedback over the course of the first year of IVE studies. Additionally, the establishment and procedures of the DRIVE governance framework have recently been explained in this video: https://youtu.be/E-PNh_z04d4

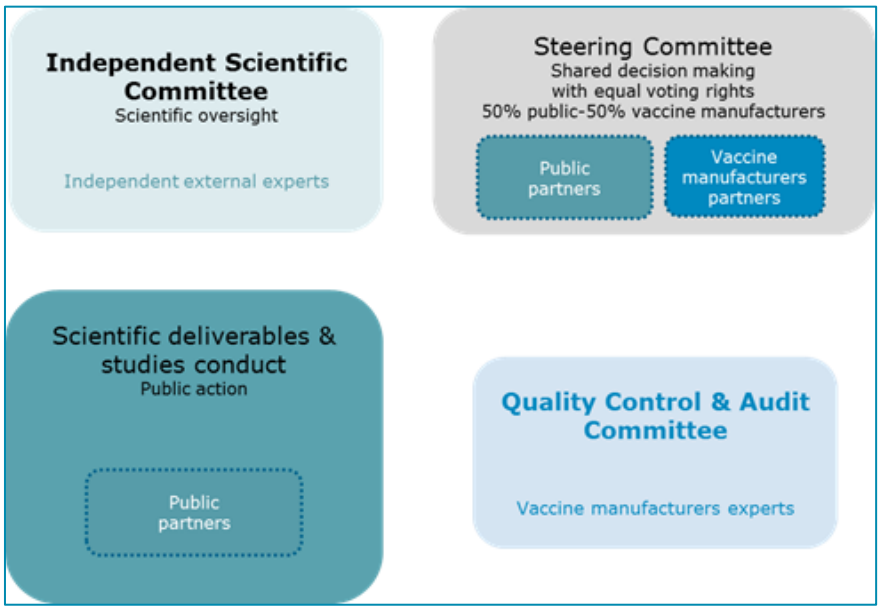

Figure 3. The DRIVE study platform for season 2019-20

Acceptability of the governance model:

To assess the success and acceptability of the proposed governance model, WP1 developed an analytic framework around six thematic areas, subdivided into 18 criteria and key performance indicators (KPIs) (please refer to D1.5 for more details). Governance criteria contain both factual information which evaluate the efficiency and accountability of the study platform (e.g.budget spent, number of studies, delivery times of study documents) and perception information which gather views from internal and external audiences on the legitimacy, participation, transparency and scientific integrity. At the first two annual meetings, held in September 2018 and July 2019, surveys were conducted to get feedback from the different stakeholders: External stakeholders, DRIVE partners, ISC and QCAC members.

The first-year evaluation (considered as a baseline) is detailed in the deliverable D1.5. In brief, 34 persons responded to the survey from the 68 participants who attended the annual meeting in Sept 2018 (50% response rate).

100% of Sites & External stakeholders and 94% of DRIVE partners considered it was important to obtain brand specific IVE data; 70% of Sites & External stakeholders and 100% DRIVE consortium partners considered the PPP model appropriate.

66% of Sites & External stakeholders and 80% of DRIVE partners considered the role of the ISC was appropriate, while 56% of Sites & External stakeholders and 71% considered the role of the QCAC appropriate. Finally, regarding the site selection process, 56% of Sites & External stakeholders and 82% of DRIVE partners regarded the process to be appropriate.

In light of these results, it was recommended to dedicate more efforts to raise awareness transparently on the way PPP is organised for DRIVE , to extend the role of the ISC and involve them in the sites selection process for scientific relevance and independent review, and to re-define or better focus the role of the QCAC, who now participates in the sites evaluations and makes recommendations for next seasons.

Regarding the project scientific integrity and ethics, 56% of Sites & External stakeholders and 87% of DRIVE partners considered the platform was robust and trustworthy, and it was agreed to make WP7 deliverables review clearer and more comprehensive. On top of that, none of the WP7 deliverables had been submitted on time until then, therefore it was clear DRIVE needed to revisit deliverable submission dates in line with seasonal performance and better anticipate runs of review. The deliverable review process has now been optimized.

Further to this, in relation to the creation of a sustainable network, 55% of DRIVE partners affirmed there had been important efforts made to onboard new research collaborators, and it was decided to organise a webinar or schedule face-to-face meetings with PHIs.

Based on the feedback received and on the experience of its implementation during the previous season, some adaptations and improvements are being applied in the governance of the Study Platform for season 2019-2020, particularly:

1. Finetuning the study platform governance by:
   - Improving evaluation (survey response rate: 50% first year)
   - Improving KPIs results
   - Scheduling regular SC meetings with ISC & QCAC
   - Developing a manuscript about monitoring and evaluation framework

2. Leveraging the study governance communication materials (video) and increasing visibility of DRIVE results

3. Increasing the size of the study platform by engaging more with PHIs, researchers & networks or expanding/further leveraging the capacity of contributing sites.

The second-year evaluation is on-going and will be fully detailed in the updated version of deliverable D1.5 (planned for April 2020). In brief, improvements have been made to get more feedback through the survey. At the Annual Forum meeting in July 2019 the response rate increased to 78% (53 responders from 68 participants). External stakeholders were surveyed live during the meeting using a tool called “Klaxoon” to

engage them more on the discussions. In addition, the study platform governance videos were showed upfront to ensure a good understanding.

Conclusions and future perspectives

DRIVE consortium has been successful in the development of a governance model to allow the collaboration between the different stakeholders through public-private partnership and has made important progress in establishing a sustainable IVE study platform that is sufficiently sized to enable brand-specific studies. Overall, most of the project objectives and milestones have been achieved without important deviations from the work plan, however, the need to:

- improve DRIVE study design by focusing and prioritizing the strategy;
- the involvement of additional study sites; and
- give more influence to the ISC in the study sites selection

was highlighted by IMI experts in their feedback report from the early project review undertaken in September 2019.

These issues were addressed at the Brainstorming Meeting between WP7 and EFPIA partners that was organized on 25th October 2019 to prepare the next season (2020-2021) and, particularly, to discuss the following aspects:

- determining optimal strategy to increase the study platform;
- prioritizing research agenda topics to investigate and propose for external collaborations;
- deciding on how to promote open data and share DRIVE data; and
- adjusting statistical analysis and timelines for next season.

The meeting was fruitful and concrete action plans were established to move on. Statistical justifications were presented by P95 to work on enlarging the best existing sites (after a specific site evaluation) and to actively approach new candidate sites with good vaccination coverage. In addition, working subgroups have been established to focus on improving the study design dealing with issues like confounding control and missing covariates, the added value of estimating the averted number of cases, cross-seasonal analysis and the possibility to focus on specific age groups and in a specific setting (potentially in hospital setting). A subgroup has also been created to work on establishing a data sharing platform to start sharing DRIVE aggregated data as an initial strategy to encourage the use of open data through Europe.

Much of the conversations focused on addressing the optimal strategies to expand the DRIVE network in order to achieve the goals of the project, since this is still one of the main challenges and one of the principal recommendations derived from the project evaluation. It was agreed that DRIVE needs both more study sites and larger studies:

- Sites with optimal characteristics were pre-identified; those sites have a good vaccine coverage, data quality and can improve the sample size (more GPs/hospitals; more swabs; more testings). Follow up discussions will be engaged for the next tender 2020/21.
- Countries/public health institutions having existing surveillance systems in place and vaccine coverage upper 40% for elderly were pre-identified. Several members of the DRIVE Consortium were appointed to organize face-to-face meetings with the top 7 of those PHIs (Belgium Sciensano, UK PHE, Netherlands RIVM, Germany RKI, Sweden PHI, Ireland HPSC and France Santé public).

The involvement of PHIs in DRIVE and the dissemination of the message that the outcomes of the project are not influenced by EFPIA interests continue to be two challenging issues that the consortium has planned to overcome through strategically planned meetings.

Regarding the involvement of the ISC, as previously mentioned, the site selection process in 2019/20 was divided into two phases: the quantitative assessment of the proposals' scientific aspects performed by the ISC and the qualitative assessment of the proposals' applicability and sustainability in DRIVE done by the SC. 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 for the strategic selection of the sites and

allocation of the budget in step 2. The two-step evaluation process is important for transparency standards and therefore the consortium will strive to have more fluent communication with the ISC to ensure their continued engagement in the review of the scope of the project and tender specifications. Indeed, a meeting between ISC and the SC has been scheduled in early January 2020 to review the evaluation criteria and the sites selection process and discuss the lessons learnt.