

# D3.4 Report on the comparison of adapted local protocols and Ethical Committee evaluation in each study site (season 2018-2019 update)

777363 – DRIVE

## DEVELOPMENT OF ROBUST AND INNOVATIVE VACCINE EFFECTIVENESS

### WP3 – Evaluation of studies' quality and feasibility

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## Publishable Summary

DRIVE carried out a web-based survey targeting the DRIVE study sites which performed the observational studies to address the IVE by vaccine brand/type in the 2018-2019 influenza season, in order to better assess differences in the ethical submission process, the feedback received by ethics committees by the study sites.

The results of the survey can be used to support the evaluation of the quality and feasibility of the studies for determining type/brand-specific seasonal influenza vaccine effectiveness, in order to identify possible obstacles, to share common principles, to improve and possibly harmonize the ethical submission process among participating study sites in the following seasons.

## List of abbreviations

CIRI-IT = Interuniversity Research Center on Influenza and other Transmissible Infections (Italy)  
 CV = Curriculum Vitae  
 DINÖ = Diagnostic Influenza Network Austria  
 DRIVE = Development of Robust and Innovative Vaccine Effectiveness  
 EC = Ethics Committee  
 ECDC = European Centre for Disease prevention and Control  
 ESSA= Electronic Study Support Application  
 FISABIO = Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana  
 GDPR = General Data Protection Regulation (EU) 2016/679  
 GP = General Practitioner  
 HUS= Helsinki University Hospital  
 HUVH = Hospital Universitari Vall d’Hebron  
 ILI = Influenza-like illness  
 IMI = Innovative Medicines Initiative  
 InFluNet = Italian national influenza surveillance system  
 ISS = Italian National Institute of Health (Istituto Superiore di Sanità)  
 IVE = Influenza Vaccine Effectiveness  
 NPS = Naso-Pharyngeal Swab  
 OPBG= Bambino Gesù Children’s Hospital  
 PHI = Public Health Institute  
 PI = Principal Investigator  
 RESCEU = REspiratory Syncytial virus Consortium in EUrope

SARI = Severe Acute Respiratory Infection

SP = Sentinel Practitioner

THL = National Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos)

TND = Test-Negative Design

UNIFI = University of Florence

VAHNSI = Valencia Hospital Network for the Study of Influenza

WHO = World Health Organization

WP = Work Package

## Background

As part of the evaluation of the quality and feasibility for conducting brand-specific seasonal influenza vaccine effectiveness (IVE) at the study site level, in DRIVE we sought to understand the ethics submissions review processes. The initial version of this deliverable D3.4 “Report on the comparison of adapted local protocols and Ethical Committee evaluation in each study site” [02 July 2018] reviewed the local protocols implemented in the season 2017-18 pilot season of DRIVE for differences and their rationale. In addition, local ethics procedures were assessed to understand potential hurdles for implementation of the IVE studies. The previous deliverable covered participating sites during the 2017-18 season (Finland, Italy and the Valencia Region in Spain), and Austria, that confirmed its participation in DRIVE by May 2018. The present deliverable also covers new sites participating in the 2018-19 season. Since the previous version of this deliverable, the DRIVE consortium developed generic core protocols for field-based influenza vaccine effectiveness (IVE) studies to be local adapted and implemented in the 2018-2019 influenza season. The current deliverable assesses differences between the local adapted protocols regarding ethical aspects and expand the data collection to all public health institutes (PHIs), and other organizations that joined the network after the 2018 DRIVE Call for Tender and participated in the brand-specific IVE as part of DRIVE in the 2018-2019 influenza season.

## Objectives

The main objective of this survey is the evaluation of possible impacts of differences and issues in the ethical submission processes on study implementations (e.g., samples’ peculiarities, timings, problems in access to data etc.) among the participating sites.

## Methods

### Survey

The survey prepared for the previous influenza season by University of Florence (UNIFI, Università degli Studi di Firenze) was updated to simplify the interviewing process and increase consistency. Topics of interest investigated were: inclusion of the study into the national influenza surveillance system, the need for ethics committee approval to conduct the IVE study, the type of ethics committee (national/regional/institutional; professionals involved), country-specific regulations to be followed, the need of obtaining informed consent from study participants, information regarding data storage, last feedback received from the ethics committee and time required to receive such feedback, info regarding the laboratories performing the specimen analyses, changes foreseen in the ethical submission process after enforcement of the General Data Protection Regulation (GDPR) (Regulation EU 2016/679). The survey can be found in **Annex 1**.

For each site the following is summarized:

- Influenza surveillance system – providing a brief description of the influenza surveillance in place at the study site
- Ethics – describing the ethics submission and approval process
- Informed consent – covering requirements for informed consent for individual study subjects

- Regulations and data protection – listing applicable regulations and considerations for subject data protection

## Expert respondents

The targeted experts were those involved in carrying out observational studies to address IVE by vaccine brand in the 2018/2019 influenza season. In scope of the survey were the countries for which data collection in DRIVE was already performed in the previous season, as well as those that joined the DRIVE network for the subsequent season (Table 1). In total the survey was issued to 11 sites.

*Table 1 Countries for which data collection in DRIVE was performed*

	Site participating in 2017-2018 influenza season	Site participating in 2018-2019 influenza season
National Institute for Health and Welfare (THL) (Finland)	x	x
Italian National Health Institute (ISS) (Italy)	x	x
Valencia Region - FISABIO-Public Health (Spain)	x	x
National Influenza Centre at Medizinische Universität in Wien (Austria)	x	x
Bambino Gesù Children's Hospital (OPBG) (Italy)		x
the Interuniversity Research Center on Influenza and other Transmissible Infections (CIRI-IT) (Italy)		x
the Helsinki University Central Hospital (HUS) (Finland)		x
Vall d'Hebron University Hospital (HUVH) (Spain)		x
University of Surrey (UK)		x
the National Institute for Infectious Diseases Matei Bals of Bucharest (Romania)		x
Department of Obstetrics & Gynaecology at the National and Kapodistrian University of Athens, School of Medicine, "Alexandra" General Hospital (Greece)		x

The survey was administered online using the SurveyMonkey tool between March 25 and April 9, 2019. It is available at the link: <https://www.surveymonkey.com/r/NRJNF7S>.

## Results

Eleven sites participated in DRIVE during the 2018-2019 season. The response rate to the survey was 100%. For most sites (58.3%), the ethics committee was institutional (Figure 1). Details on the respondents and on the questions are summarized in Table 3.

Which ethics committee has been consulted?

Answered: 12 Skipped: 0

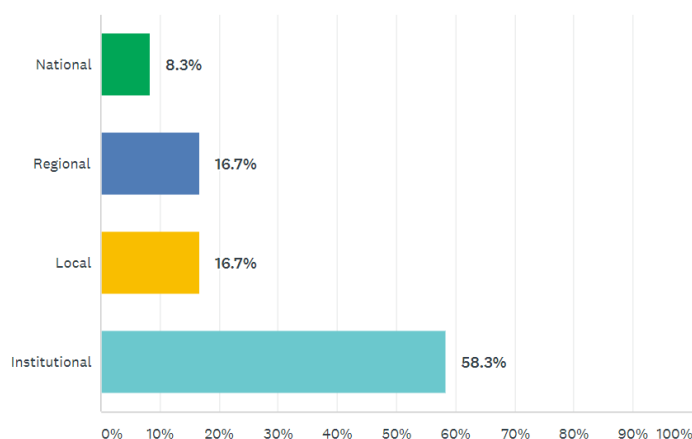


Figure 1 - Type of ethics committee consulted

## Austria

### a. Influenza surveillance system

Influenza virus activity in Austria is monitored, within the frame of the Austrian Influenza Sentinel Network, by the Diagnostic Influenza Network Austria (DINÖ), a group of sentinel physicians throughout Austria, which collect clinical nasopharyngeal swab (NPS) samples, as well as epidemiological information. It allows not only to detect the beginning, the peak and the end of the epidemic influenza virus activity in Austria, but also to estimate the annual impact of the influenza virus epidemic activity on the Austrian population. Within this sentinel network in Austria, nasopharyngeal swabs are collected from selected patients with acute influenza infections during the influenza season. Specimens are sent to the Centre of Virology at the Medical University of Vienna (National Reference Laboratory) and investigated for the presence of influenza viruses and to identify the type, subtype and strain. Every year a retrospective statistical analysis of fully anonymized viral and epidemiological data is performed. NPS-samples of patients for which vaccination status is missing are excluded from IVE estimates.

### b. Ethics

The approval of the ethics committee for the study is only valid for the duration of one year, for this reason each season an amendment is needed. Since the approval for the conduction of the study for the season 2018-2019 was valid until 05.05.2019, an amendment for the following season at the time of completion of the survey (April 2019) was foreseen at the earliest three weeks before the expiration of such approval. The feedback received from the ethics committees on the protocol used in the last



influenza season was positive. Usually, about two months are required, every year, to receive the approval by the ethics committee. The investigators needed to submit the documentation to the ethics committee by May 2018. The ethics committee<sup>1</sup> is based at the Medical University of Vienna and composed of clinicians, psychologists, lay persons, pharmacologists, general practitioners, paediatricians, microbiologists, biostatisticians, pharmacists, experts in legal and insurance matters or a coroner, experts in bioethics, representatives of patient associations. The documents that are to be submitted to the ethics committee comprise the study protocol, the declaration of sponsorship, the Principal Investigator (PI)'s declaration, the curriculum vitae (CV) of the PI and the declaration on conflicts of interest.

#### **c. Informed consent**

Informed consent was not required at the subject level, as data are fully anonymized.

#### **d. Regulations and data protection**

Written procedures for data protection exist at the organizational level, but no data management plan is available at the study level.

## **Finland**

### **1. THL**

#### **a. Influenza surveillance system**

During the 2018-2019 influenza season, THL, the Public Health Institute of Finland, performed a population-based study which made use of secondary data from existing health care databases. The study was part of the national routine practice for assessing influenza vaccine effectiveness by using data derived from the National Vaccination Register (all vaccinations administered in public primary health care), National Infectious Disease Register (all influenza findings from all laboratories) and Register of Primary Health Care Visits (all public primary health care visits), complemented with data from other routine administrative registers.

#### **b. Ethics**

Since the cohort performed by THL made use of secondary data from routine databases, an ethical evaluation was not mandatory, according to the relevant regulations. However, the investigators nevertheless requested an evaluation from an institutional ethical review group, mainly composed of clinicians and experts in legal and insurance matters or coroners (the composition of the institutional ethical work group varies). THL Ethical Review Group has no public website, as it is for internal use of the institute and only reviews projects conducted by THL that do not need an 'official' ethics committee review. The documents submitted to the THL ethics committee were the cover letter by the principal and other investigators, the protocol, including a summary, the principal investigator's judgement on the ethical aspects of the study, including its scientific relevance, risks for the study subjects and other ethical issues associated with the conduction of the study, information on the samples to be collected, the scheme of data management, data protection, retention time, archiving,

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<sup>1</sup> <http://ethikkommission.meduniwien.ac.at/>

and the description of the personal data file (According to §10 of the personal Data Act 523/1999). When consulted, the institutional ethics committee provides clearance within about four weeks. In addition, an approval was needed from all register controllers of the used registers. At the moment of participation in the survey (April 2019), no change in the institutional ethical submission process was implemented since the enforcement of the reform of EU data protection rules (GDPR, Regulation (EU) 2016/679) in May 2018.

### **c. Informed consent**

The registers cover all citizens of Finland. Citizens are informed in general about the use of data by means of the publicly available 'Privacy Notice for Scientific Research'. For the conduct of the specific studies based on the registry-, subjects are not contacted and the collection of informed consent from the study subjects is not required.

### **d. Regulations and data protection**

Data are pseudonymised for analyses in THL. Since sharing individual personal data out of THL is not allowed, data are anonymised by aggregation.

The following are the main country-specific regulations that are to be followed to perform register-based IVE studies in THL and allow using as many data sources as possible and assure patients privacy protection:

- Data protection Act 1050/2018 (before 1.1.2019 Personal Data Act 523/1999)
- Act on the Openness of Government Activities 621/1999
- Communicable Diseases Act 1227/2016
- Act on the National Institute for Health and Welfare 568/2008
- Population information act 661/2009
- The Statistics Act 280/2004
- Act on the electronic processing of customer data in social and health care 159/2007
- Act on Electronic Prescription of Medicines 61/2007
- Act on National Personal Records Kept under the Health Care System 556/1989
- Health insurance act 1224/2004
- National Pensions Act 568/2007
- Act on inquest (examination of the reason for death 459/1973
- Act on the position and the rights of the patient 785/1992
- Act on the position and the rights of the customer of the social welfare services 812/2000
- Act on the statistics measures of the National Research and Development Center for Welfare and Health (now under THL) 409/2001
- Archives Act 831/1994
- All relevant Decrees complementing these acts

The laws/guidelines that apply to the transfer of data to DRIVE are General Data Protection Regulation, 679/2016/EU and the Data protection Act 1050/2018 (before 1.1.2019 Personal Data Act 523/1999). Permissions of the Register Controllers of the registers are required.

Most of the abovementioned regulations also apply to the rights of the data subject.

Study subjects are explicitly informed about the use of data by means of the publicly available 'Privacy

Notice for Scientific Research'.

## 2. Helsinki University Hospital (HUS)

### a. Influenza surveillance system

The effectiveness of seasonal influenza vaccine against laboratory-confirmed influenza infection requiring hospitalization has been assessed by the Helsinki University Hospital (HUS) among adults during influenza season 2018-2019 through a test-negative case-control study.

### b. Ethics

Regarding authorizations/clearances/permissions (e.g. from a regional/national data protection officer), patients' informed consent, favourable opinion of the Ethics committee and the Institutional approvals of HUS, THL and the municipalities of Espoo, Kirkkonummi and Kauniainen were required. The study received approval from the Local Ethics committee of the Helsinki University Hospital. (<https://www.hus.fi/tutkijalle/tutkimuseettiset-toimikunnat/Sivut/default.aspx>) approximately seven weeks after submission of the documentation, which occurred in August 2018. The EC is composed of clinicians, psychologists, lay persons, general practitioners, paediatricians, biostatisticians, experts in legal and insurance matters or coroners, representatives of patient associations. The documents that are to be submitted to the ethics committee are the patient information sheet, the informed consent form/the authorized representative form, the CV of the PI, the PI declaration, the liability insurance, study budget, study protocol, and also an application form, a covering letter, a protocol summary in Finnish, DRIVE TND core protocol, information sheet and consent form for next of kin (both in Finnish and Swedish), the justification for the consent procedure, a privacy statement for scientific research, evaluation of risks for privacy, and an ethical evaluation by the PI.

Written consent is needed from patients participating in the study. Minor changes were required by the EC to the informed consent form and patient information leaflet.

Ethics committee did not require amendments to the protocol but HUS and THL required amendment to the study protocol to share register controller responsibility and a new review by the ethics committee was necessary because of the changes made. To pseudonymise data, the personal identity code is replaced by a study code in study forms and databases, the key register being stored separately, protected by specific access code.

Changes in the ethical submission process that were implemented since the enforcement of the GDPR Regulation (EU) 2016/679 concerned the information that had to be updated in the study information leaflet and the informed consent form, and the previous description of the personal data file was replaced with a privacy statement for scientific research. Finally, a written evaluation of privacy risks was required.

### c. Informed consent

Participating subjects receive written and oral information of the study in a language they understand before they sign an informed consent at the enrolment.

#### **d. Regulations and data protection**

The country-specific regulations followed to perform the study (unofficial translations) were:

- Medical Research Act (488/1999)
- Personal Data Act 523/1999, since 1.1.2019 Data protection Act 1050/2018
- Act on the Openness of Government Activities 621/1999
- Act on the Status and Rights of Patients 785/1992
- Patient Injury Act 585/1986-
- Act on National Personal Records Kept under the Health Care System 556/1989
- Act on the National Institute for Health and Welfare 668/2008
- Archives Act 831/1994
- All relevant Decrees complementing these acts

For the transfer of data to DRIVE the General Data Protection Regulation, 679/2016/EU and Personal Data Act 523/1999 (since 1.1.2019 Data protection Act 1050/2018) applied.

The laws/guidelines that apply to the rights of the data subject are:

- Directive 2001/20/EC
- Medical Research Act (488/1999)
- General Data Protection Regulation, 679/2016/EU
- Personal Data Act 523/1999, since 1.1.2019 Data protection Act 1050/2018
- Act on the Openness of Government Activities 621/1999
- Act on the Status and Rights of Patients 785/1992
- Patient Injury Act 585/1986
- Act on National Personal Records Kept under the Health Care System 556/1989
- All relevant Decrees complementing these acts

## **Greece**

#### **a. Influenza surveillance system**

The Alexandra General Hospital in Athens conducted a prospective cohort study to estimate the effect of vaccinating with the quadrivalent vaccine pregnant women during the third trimester of pregnancy on the occurrence of laboratory-confirmed influenza in women themselves and their babies <6 months of age.

#### **b. Ethics**

Permission was obtained from the Institutional Ethics Committee of the hospital composed of clinicians and one midwife, one radiotherapist and one technician. The Ethics Committee assessed the study protocol, the patient information sheet, and the informed consent form. Approval was received approximately 3 weeks after the submission of the documentation in September. No amendments nor administrative changes to the protocol were requested by the EC. The GDPR Regulation (EU) 2016/679 was applied to the rights of the data subject.

#### **c. Informed consent**

Written informed consent was requested from all participants, who were informed about the study aims and procedures.

#### **d. Regulations and data protection**

To perform the study no specific regulations, except the GDPR Regulation (EU) 2016/679, had to be followed.

## **Italy**

### **1. Italian National Institute of Health (ISS)**

#### **a. Influenza surveillance system**

In Italy, annual influenza vaccination targets persons aged 65 years or above and high-risk subjects. A TND case-control study to assess IVE coordinated by the National Health Institute ISS was conducted under the national influenza surveillance system (InfluNet) that includes the epidemiological and virological influenza surveillance systems and which was based on the reports by a sample of sentinel GPs. InfluNet was first implemented in Italy in the 1999/2000 influenza season and is based on the reporting activity by sentinel practitioners (general practitioners and paediatricians). The system aims to monitor the incidence of influenza-like illness, define the extent of the seasonal epidemics, and collect information on circulating strains. Sentinel practitioners are asked to report weekly influenza like illness cases (according to the EU ILI case definition) occurring during the year, using standardised forms. Specific information regarding age and influenza vaccine status are collected and reported using web-based electronic Case Report Forms<sup>2</sup>. For surveillance of circulating virus strains sampling kits are sent out to regional coordinators for surveillance. Specimens are tested at the regional Reference Laboratories distributed in the Italian regions. Results are collected and reported using web-based electronic case reporting forms from the National Influenza Centre.

Analysis is performed weekly and published by the ISS and the Ministry of Health on their respective websites.

#### **b. Ethics**

No changes in the ethical submission process have been implemented since the enforcement of the new reform of EU data protection rules (GDPR, Regulation (EU) 2016/679) in May 2018. Although an Ethics Committee approval is not mandatory since the data collection is part of the National Influenza Surveillance System, the study was submitted to ISS Ethics Committee during the 40<sup>th</sup> week of the year 2018 and approved in week 47 on November 23<sup>rd</sup>, 2018. The national ethical committee is based at the ISS and composed of pharmacologists, general practitioners, paediatricians, pharmacists, experts in legal and insurance matters/coroners, experts in bioethics, epidemiologists and geneticists. In addition to the study protocol, the documents that were submitted to the ethics committee comprised the CV of the PI, the study budget, and a summary of the protocol. Approval is expected in approximately four weeks after the submission of the documentation.

#### **c. Informed consent**

Study participants are requested an oral consent to participate in the study.

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<sup>2</sup> <https://old.iss.it/site/RMI/imove/default.aspx?ReturnUrl=%2fsite%2frmi%2fimove%2f>

#### **d. Regulations and data protection**

To perform the study no specific regulations, except the GDPR Regulation (EU) 2016/679, had to be followed.

## **2. Bambino Gesù Children Hospital (OPBG)**

#### **a. Influenza surveillance system**

At the Bambino Gesù Children Hospital a test-negative case control study was performed with the aim of measuring effectiveness of the vaccines against severe acute respiratory infections (SARI). In this study, the study population is represented by the community-dwelling children with no contraindication for influenza vaccination hospitalised for SARI.

#### **b. Ethics**

The local ethics committee is composed of clinicians, pharmacologists, paediatricians, general practitioners, microbiologists, biostatisticians, pharmacists, experts in legal and insurance matters/coroner and an expert in bioethics, representatives of patient associations and medical examiners and epidemiologists. In addition to the study protocol, the documents that were submitted to the ethics committee comprised the patient information sheet, the informed consent form, the authorised representative form, the declaration of sponsorship, the PI declaration, the curriculum vitae of the PI, the declaration on conflicts of interest, and the liability insurance. The documentation was submitted in July to the local (hospital) Ethics Committee. Approval was received approximately 3 weeks after the submission of the documentation. No amendments nor administrative changes to the protocol were requested by the EC.

#### **c. Informed consent**

Study participants were requested to sign the written informed consent form. Study subjects are explicitly informed about the use of data in the Patient Information sheet.

#### **d. Regulations and data protection**

The regulation to be followed to perform IVE studies at the OPBG is the GDPR Regulation (EU) 2016/679.

## **3. Interuniversity Research Center on Influenza and other Transmissible Infections (CIRI-IT)**

#### **a. Influenza surveillance system**

CIRI-IT supervised two population-based studies, one cohort study and one test-negative case-control study.

The aim of the cohort study was to estimate IVE against medically attended laboratory-confirmed

influenza by vaccine brand and overall influenza vaccination in healthcare workers at Hospital Policlinico San Martino Genoa and at the research and teaching hospital placed in Milan Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Fondazione). All healthcare workers of the two hospitals were strongly invited to participate to the cohort study. The study population cohort consisted of healthcare workers of the two Italian hospitals.

The second study was a case-control study in which the study population consisted of patients aged six months and above, with no contraindication for influenza vaccination, who consulted the GPs or paediatricians and were recruited in the study for ILI-related conditions.

#### **b. Ethics**

The approval by the regional ethics committee was required for performing both studies. The EC was regional and composed of clinicians, psychologists, lay persons, pharmacologists, general practitioners, paediatricians, microbiologists, biostatisticians, pharmacists, experts in legal and insurance matters/coroners, experts in bioethics, representatives of patient associations, nutritionists, biomedical engineer, geneticists, experts in occupational health safety. In addition to the study protocol, the documents that were submitted to the ethics committee comprised the patient information sheet, the informed consent form, the declaration of sponsorship, the PI declaration, the curriculum vitae of the PI, the study budget.

The documentation for both studies was submitted in July 2018 to the Regional Ethics Committee. Endorsement from the EC was obtained after six weeks. A revision of the protocol was required by the EC only with regards to the cohort study: the ethics committee requested to describe in more detail the method for calculating the sample size (significance level was set at 5% and the test power at 90%, considering a possible drop-out rate after recruitment of 10% and with a minimum coverage rate of 15%, a sample of 5183 subjects, 676 of whom vaccinated, was calculated as sufficient for the study). The study protocol was subsequently amended as per EC request.

#### **c. Informed consent**

Written consent from participating subjects was required for both studies.

#### **d. Regulation and data protection**

The regulation to be followed to perform population-based studies, cohort study and test-negative case-control study is the GDPR Regulation (EU) 2016/679.

## **Romania**

#### **a. Influenza surveillance system**

National Institute for Infectious Diseases "Prof. Dr. Matei Bals", Bucharest, Romania performed a test-negative case-control study design. The study population consists of patients aged 6 months and older, with no contraindication for influenza vaccination, admitted to hospital in the National Institute for Infectious Diseases "Prof. Dr. Matei Bals" with SARI. The study catchment area is Bucharest and the area comprising Ilfov, Dambovită, Giurgiu, Prahova, Argeş, Teleorman, Ialomița, Dolj, Valcea, Olt. Data were collected using a standardized questionnaire/data collection form. The sources for the



current and previous vaccination status and for collecting general data are hospital medical records, consultation of the patient's vaccination card, interview with patient or his/her family, interview with patient's GP (according with rules for Vaccination Status Ascertainment), interview with patient's attending physician.

#### **b. Ethics**

Single centre studies require authorization from the institutional review board and the institutional bioethics committee. The study received approval from the institutional ethics committee, composed of clinicians, psychologists and experts in bioethics one week after submission of the documentation, which occurred in September. The documents that were submitted to the ethics committee were the study protocol, patient information sheet, informed consent form and the CV of the principal investigator. No amendments nor administrative changes were required by the EC.

Changes in the ethical submission process that were implemented since the enforcement of the GDPR Regulation (EU) 2016/679 consisted in ensuring that the informed consent form is compliant with GDPR; patients are informed of their rights guaranteed by GDPR.

#### **c. Informed consent**

Informed consent was obtained from each patient prior to performing any study specific procedure, according to the Institute's Standard Operating Procedures, namely:

- consent to be obtained directly from all patients who are adults, conscious, and able to provide written informed consent;
- consent to be obtained directly in the presence of an impartial witness from all patients who are adults, conscious, but unable to read/write;
- consent to be obtained from at least one of the parents/legal representative for minors;
- consent to be obtained from next of kin/legal representative for patients who are unconscious or otherwise unable to understand the nature of the study.

#### **d. Regulations and data protection**

The following are the regulations that are to be followed to perform IVE studies that apply to the transfer of data to DRIVE and to the rights of the data subjects (unofficial translation):

- Law no. 677/2001 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
- Law no. 95/2006 on health reform
- Law no. 46/2003 on patient's rights
- Order of MSP no. 386/2004 on the approval of the Norms for the application of the patient's rights law no. 46/2003
- International Commission for Accreditation Standards for Hospitals,
- 5th Edition, 2014, GLD 15,16,17,18,19, HRP 7
- Law no. 16/1996 of 2 April 1996. The Law of National Archives. Instructions for use.
- Law no. 358/2002, amending and supplementing the Law on National Archives no. 16/1996
- Emergency Ordinance 39/2006 to amend and complete the Archives Act
- National no. 16/1996
- Law no. 474/2006 regarding the approval of Government Emergency Ordinance no. 39/2006 for amending and completing the Law



- National Archives no. 16/1996
- EU General Data Protection Regulation (GDPR) from 14 April 2016 enforced on 25 May 2018.
- International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva.
- Council for International Organizations of Medical Sciences (CIOMS); 2016.
- ICH GCP E6(R2)
- Local institutional codebooks, regulations and SOPs

## Spain

### 1. Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, (FISABIO)

#### a. Influenza surveillance system

Since 2009, FISABIO (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana) has conducted a hospital-based test-negative case control study applying an active annual surveillance scheme in the Valencia Hospital Network for the Study of Influenza (VAHNSI) to monitor influenza virus epidemiology and its impact across different age and risk groups. For the 2017-2018 influenza season FISABIO enlarged the time window of the VAHNSI study from 1<sup>st</sup> of September to 30<sup>th</sup> of June (4 months longer than before) to capture, from September to June, (10 consecutive months) admissions with laboratory confirmed (RT-PCR), respiratory syncytial virus and their seasonality with confidence. For the 2018/2019 season, FISABIO conducted this study during all the year (September to August) and the European Centre for Disease prevention and Control (ECDC) ILI-case definition (at least one systemic symptom: fever, malaise, headache or myalgia and one respiratory symptom: cough, sore throat or respiratory difficulty within the 7 days prior to admission) was replaced by the World Health Organization (WHO) SARI-case definition (cough within 10 days prior to admission) for better adapting its participation in the RESCEU project.

#### b. Ethics

The study was first approved for one influenza season in 2009. In 2011 the protocol for the conduction of IVE studies was slightly changed and approved; since then, annual renewal requests have been made to the Ethics Committee before each influenza season. For the study to be performed, the study protocol was accepted by the Ministry of Health and by the Public Health Ethics Research Committee (Comité Ético de Investigación de la Dirección General de Salud Pública y Centro Superior de Investigación en Salud Pública (CEI DGSP-CSISP)<sup>3</sup>. It took approximately six weeks to receive the approval after the submission of the documentation to the ethics committee, composed by clinicians, pharmacologists, general practitioners, paediatricians and experts in legal and insurance matters/coroners. After the first approval in 2011, the study protocol is updated annually and sent for the revision to the Ethics Committee. In addition to the study protocol, the documents that were submitted to the ethics committee comprised the informed consent form, the informed assent form and the authorized representative form.

<sup>3</sup> <http://grupos.fisabio.san.gva.es/web/rvb/comite-de-etica>

### **c. Informed consent**

For the 2018/2019 influenza season, written informed consent was gathered before enrolling patients into the test-negative design study. Patients enrolled include non-institutionalized patients, inhabiting continuously in the participating hospitals catchments' area for at least the previous six months, able (or her/his legal tutor) to give informed written consent, and that remain in the hospital for at least 24 hours.

As far as the informed consent form is concerned, two different documents were prepared, depending on the age of the subjects to be enrolled. One is administered to patients >18 years. For patients <12 years, the informed consent form has to be read and accepted by parents or legal tutors. In case study subjects are aged between 12 and 18 years, one informed consent (assent) is to be signed by the patients, another one by their parents/legal tutors.

In the informed consent the objectives of the study are described, as well as the nature of processed data (aggregated), the recipients of possible data transfers (FISABIO Research Centre), the rights of data subjects (in particular, the possibility to withdraw at any time without the need to provide justification) and the consequences of not participating in the study. It is specified that the study is carried out according to the following ethical regulations: updated Declaration of Helsinki and Standards of Good Epidemiological Practice and that personal data are treated in accordance to Law 15/99 "Protección de Datos de Carácter Personal".

### **d. Regulations and data protection**

The country-specific regulations to be followed to perform IVE studies is the post-authorization studies law ORDEN SAS/3470/2009. The Ethics Committee authorization is needed for the transfer of data to DRIVE consortium. The GDPR, Regulation (EU) 2016/679 apply for the rights of the data subjects. Study subjects are explicitly informed about the use of data during the interview and before signing informed consent. FISABIO received the approval to share data with the Global Influenza Hospital Surveillance Network (<https://www.gihsn.org/>), a platform aimed to generate strong epidemiological and medical evidence on the burden of severe influenza and the public health impact of influenza vaccines. The platform is in place since 2011, it gathers several sites throughout the world and is affiliated with national health authorities.

Specimens are not transported outside of the FISABIO laboratory.

Since the enforcement of the GDPR Regulation (EU) 2016/679 in 2018, the changes in the ethical submission process that was implemented consisted in adding to the informed consent an appendix informing about the new data protection law. Data of participating patients are fully anonymized.

## **2. Hospital Universitari Vall d'Hebron (HUVH)**

### **a. Influenza surveillance system**

Hospital Universitari Vall d'Hebron (HUVH) participated as a study site (as "sentinel centre") in a multicentre project developing an observational case-control study using a test-negative design. Patients admitted to HUVH due to influenza-like illness or laboratory-confirmed influenza aged 6 months and above, with no contraindication for influenza vaccination, and belonging to the Institut Català de la Salut, the main institution of Catalonia's public healthcare system and the owner of HUVH, constitute the population. To obtain the information about the vaccine, the vaccination record available in the primary healthcare electronic clinical record of Catalonia (ECAP), the electronic

clinical record of the hospital or the patients' vaccination card were used. In case no data about influenza vaccination were available in these resources, the electronic clinical record of HUVH or the vaccination card, patients and/or their relatives were interviewed. When positive vaccination status was indicated only by recall or was otherwise ambiguous, the vaccination status was coded as "potentially vaccinated". The information regarding the vaccine brand and the type of vaccine administered was obtained from the vaccine providers of the Public Health Agency of Catalonia.

#### **b. Ethics**

The Ethics committee which was consulted for approval was the institutional one, the Clinical research Ethics Committee ([http://en.vhir.org/portal1/article\\_menu\\_comites.asp?contenttypeid=317&contentid=1313&sub=347&t=ceic](http://en.vhir.org/portal1/article_menu_comites.asp?contenttypeid=317&contentid=1313&sub=347&t=ceic)), composed of clinicians, lay persons, pharmacologists, paediatricians, pharmacists, experts in legal and insurance matters/coroners and experts in bioethics. Only the study protocol was sent to the EC for revision.

#### **c. Informed consent**

Since no intervention that it is outside the usual practice of the Hospital Universitari Vall d'Hebron during the flu season is required to perform the study, the informed consent form from patients is not needed.

#### **d. Regulations and data protection**

Orden SAS/3470/2009, available at: [http://www.vhir.org/global/pdf/ceic/SAS\\_3470\\_2009.pdf](http://www.vhir.org/global/pdf/ceic/SAS_3470_2009.pdf), is the country-specific regulation to be followed to perform the study. All the information obtained in the study are treated in compliance with the European GDPR Regulation 2016/679. The Real Decreto 1720/2007 (available at: <http://www.vhir.org/portal1/Global/pdf/ceic/2018/RD1720-2007-Reglamento-LOPD.pdf>) is the decree that apply to the transfer of DATA to the DRIVE Consortium, as well as the European GDPR Regulation 2016/679. The same two laws also apply to the rights of data subjects.

The information about the use of the data to data subjects is arranged through a specific waiver by the Ethics Committee. The database is filled in at the investigational site and is accessed by the investigator and the supporting site staff. Data are pseudonymized. The study site is the owner of the data and may disseminate the study results according to their local practices.

## **United Kingdom**

#### **a. Influenza surveillance system**

University of Surrey conducted a test-negative case control study to explore the feasibility of delivering a new testing service in primary care and calculate influenza vaccine effectiveness.

#### **b. Ethics**

UK national research ethics committee regulations were followed.

The study received approval from the National Ethics Committee, the Research Ethics Service and Research Ethics Committees (<https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-ineed/research-ethics-committee-review/applying-research-ethics-committee/>), composed of clinicians, lay persons, paediatricians, experts in bioethics and representatives of patient associations approximately 12 weeks after submission of the documentation, which occurred in July. The documents that were to be submitted to the ethics committee were the study protocol, patient information sheet, informed consent form, informed assent form, authorized representative form, the declaration of sponsorship, the declaration on conflict of interest, the CV of the PI, the liability insurance and the study budget. Minor changes were required by the EC to the informed consent form and patient information leaflet: additional leaflets were required to target specific child age groups. For this reason, the study was approved only at the beginning of February and this delay resulted in a lower number of subjects contributed to the pooled analysis of the DRIVE project. To anonymize data, all identifiers were removed at source by a third-party data extraction organisation and transferred via secure data networks to the University of Surrey secure servers. Changes in the ethical submission process that were implemented since the enforcement of the GDPR (Regulation (EU) 2016/679) consisted in providing additional information on patient information sheets to make it clear how data is processed.

#### c. Informed consent

The subjects were informed about the use of their data by posters in the general practice. Those participating in the point of care studies were given detailed information leaflets and gave written consent to study participation. Patients could opt out anytime during the study.

#### d. Regulations and data protection

For the transfer of data to DRIVE the GDPR 679/2016/EU was applied; data were requested to the Royal College of General Practitioners Research and Surveillance Centre scientific committee. The laws/guidelines that apply to the rights of the data subject is the GDPR 679/2016/EU.

In Table 2 Ethics committee clearance's date are reported for the various ethics committees. The main characteristics of the ethical submission process in countries that have conducted IVE studies in the 2018-2019 influenza season and that participate in DRIVE are summarized in Table 3.

*Table 2. DRIVE 2018/19 study sites: ethics committees and date of approval*

Site	Country	Ethics committee	Date of approval
MUV	Austria	Ethics committee of the MUV	May 4, 2018
HUS	Finland	Regional Ethics Committee of the Expert Responsibility Area of Helsinki University Hospital	Nov 14, 2018
THL	Finland	Institutional review board of the National Institute for Health and Welfare, Finland	June 2, 2016
UoA	Greece	Ethics Committee of the "Alexandra" General Hospital of Athens	Oct 16, 2018

BIVE-HOSP	Italy	Ethics committee of the Bambino Gesù Children's Hospital, Rome Ethics committee of the Sant'Andrea Hospital, Rome Ethics committee of the University Hospital, Bari Ethics committee of the San Martino Hospital, Genova Ethics committee of the Le Scotte Hospital, Siena	Sept 2018 (all committees)
CIRI-IT (TND)	Italy	Ethics committee of the Liguria Region	Oct 1, 2018
CIRI-IT (HCW)	Italy	Ethics committee of the Liguria Region	Oct 1, 2018
ISS	Italy	Not required, but submitted to ISS Ethics committee for information	Nov 23, 2018
NIIS	Romania	Bioethics committee of the NIIS	Nov 12, 2018
FISABIO	Spain	National Ethics Committee	Dec 21, 2009 (for the first season), updated in 2011 for the following seasons
HUVH	Spain	Comité Ético de Investigación Clínica del Hospital Universitari Vall d'Hebron	Dec 13, 2018
RCGP RSC	UK	NRES Committee West Midlands, Solihull. IRAS project ID: 252081, REC reference: 19/WM/0015	Feb 4, 2019

Table 3 Characteristics of the ethical submission process in countries that have conducted IVE studies in the 2018-2019 influenza season and that are part of the DRIVE network

	Austria	Finland		Greece	Italy			Romania	Spain		UK
		THL	HUS		Study nested into national surveillance system (ISS)	Hospital-based study (OPBG)	CIRI-IT		FISABIO (hospital)	Vall d'Hebron	Surrey
<b>Study nested into national influenza surveillance system (yes/no)</b>	Yes	No	No	No	Yes	No	No	No	No	Yes	Yes
<b>The study made use of secondary data from routine databases (yes/no)</b>	No	Yes	No	No	Yes	No	No	Yes, for ascertainment of vaccination and health status	No	Yes	No
<b>Ethics committee approval required for performing IVE studies each season (yes/no)</b>	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No, only the first season (in 2011)	Yes	Yes
<b>Informed consent needed (yes/no)</b>	No	No	Yes, written	Yes, written	Yes, oral	Yes, written	Yes, written	Yes, written	Yes, written	No	Yes, written
<b>Dates in which the investigators need to submit the documentation to the ethics committee</b>	May	N.A.	August	September	October	July	July	September	August	September	July
<b>Ethical committee used (national/regional/local/institutional)</b>	Institutional	Institutional	Institutional	Institutional	National (Institutional)	Local	Regional	Institutional	Institutional	Local	National
<b>Feedback received from the</b>	Approved	Approved	Approved	Approved	Approved	Approve	Approve	Approved	Approved	Approved	Approved

	Austria	Finland		Greece	Italy			Romania	Spain		UK
ethics committees on the protocol used in the last influenza season (approved/ not approved/ approved after revision of the protocol)			after minor revisions			d	d (case-control study) Approved after protocol revision (cohort study)				
Amendments or administrative changes to the study protocol required by Ethics Committee	Yes (only updating the timeframe of the study)	N.A.	No <sup>4</sup>	No	No	No	Yes, better description of sample size calculation required for the cohort study	No	No	No	Yes, changes to patient information leaflets and consent forms required to add leaflets to target specific child age-groups
Time needed to receive approval by the ethical committee (in weeks)	8	4	7	3	4	3	6	1	4	4	12
Ethics approval process resulted in a delay compared to the expected timing	No	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
Study involve sending biological	No	No	Yes	Yes	Yes	No	No	No	No	No	No

<sup>4</sup> Ethics committee did not require amendments to the protocol but HUS and THL required amendment to the study protocol to share register controller responsibility and a new review by the ethics committee was necessary because of the changes made.

	Austria	Finland		Greece	Italy			Romania	Spain		UK
<b>samples outside the institution/abroad</b>											
<b>Personal information are anonymized or pseudonymized and security of all data is guaranteed by normalized procedures (yes/no)</b>	Yes	Yes	Yes	Yes	Yes (during data analysis, not in data collection)	Yes	Yes	Yes	Yes	Yes	Yes

IVE: influenza vaccine effectiveness; N.A. = Not Available.



## Discussion and Conclusions

Ethics committee clearance was required for yearly IVE assessment, with the exception of Finland THL and Italy ISS where it was not required but it was sought nonetheless, and Spain FISABIO, that obtained approval for the first year in 2011. In 4 study sites (33.3%: Austria, Italy ISS, UK, Spain HUVH), studies were nested into the national influenza surveillance system; secondary data from pre-existing national routine administrative registers were used in 4 sites (33.3%: Finland THL, Italy ISS, Romania, Spain HUVH).

Clinicians, paediatricians and legal/bioethics experts were the most represented components in the ethics committees, followed by pharmacologists, general practitioners and lay people/patients' representatives (**Figure 2**). Among the documents to be submitted to the ethics committee, the study protocol was mandatory in all cases (100%), followed by the Principal Investigator CV (72.7%) and the informed consent form (72.7%), patient information sheet was needed in 63.6% of cases (**Figure 3**). Informed consent, either written (66.7%) or oral (8.3%), was obtained in 75% of cases.

Which of these professionals compose the ethics committee?

Answered: 12 Skipped: 0

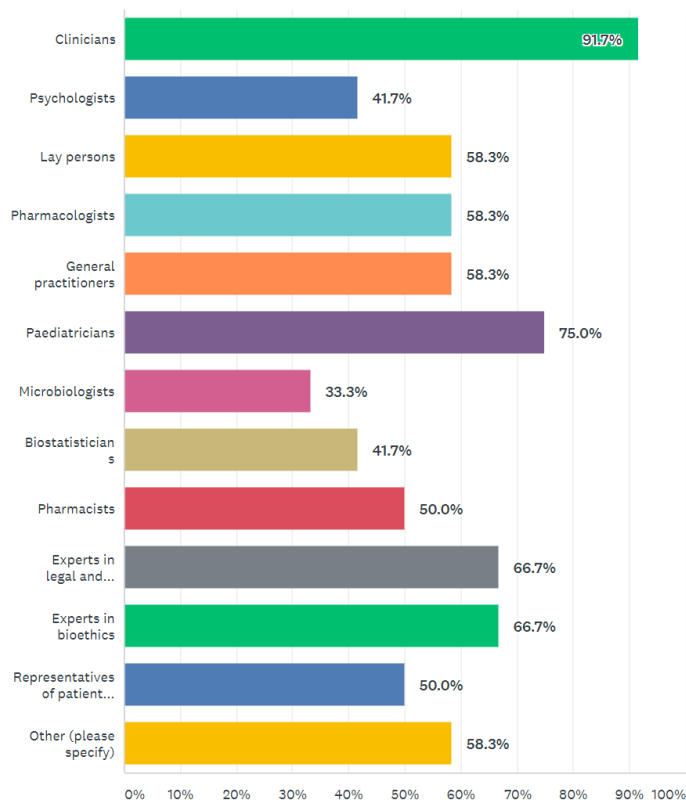


Figure 2 - Professional figures members of ethics committee

What are the documents that need to be submitted to the ethics committee?

Answered: 11 Skipped: 1

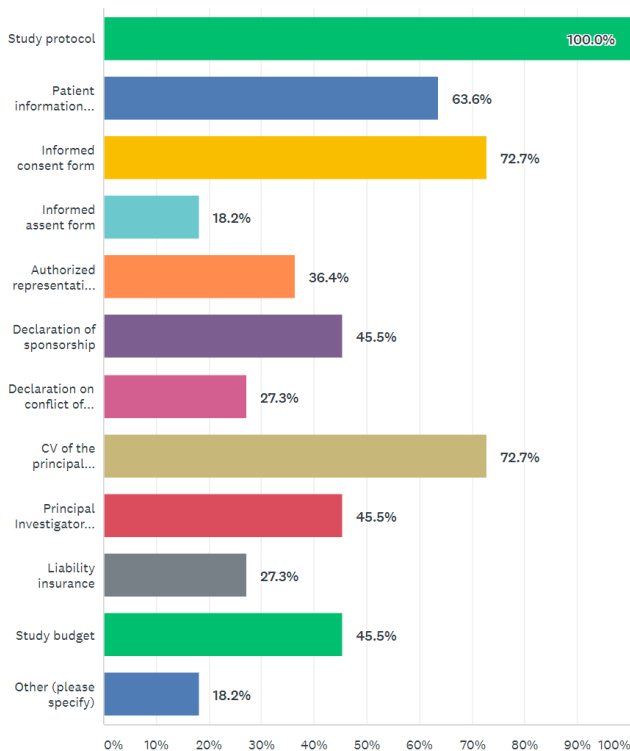


Figure 3 - Documents submitted to the ethics committee

Study protocols were approved by the ethics committee in 83.3% of cases, while in two study sites, namely CIRI (Italy) and University of Surrey (UK), protocols were approved after a revision consisting of minor changes. The submissions to ethics committee were mostly performed during summer, before the beginning of Influenza season, with 40% of studies submitted in July (**Figure 4**).

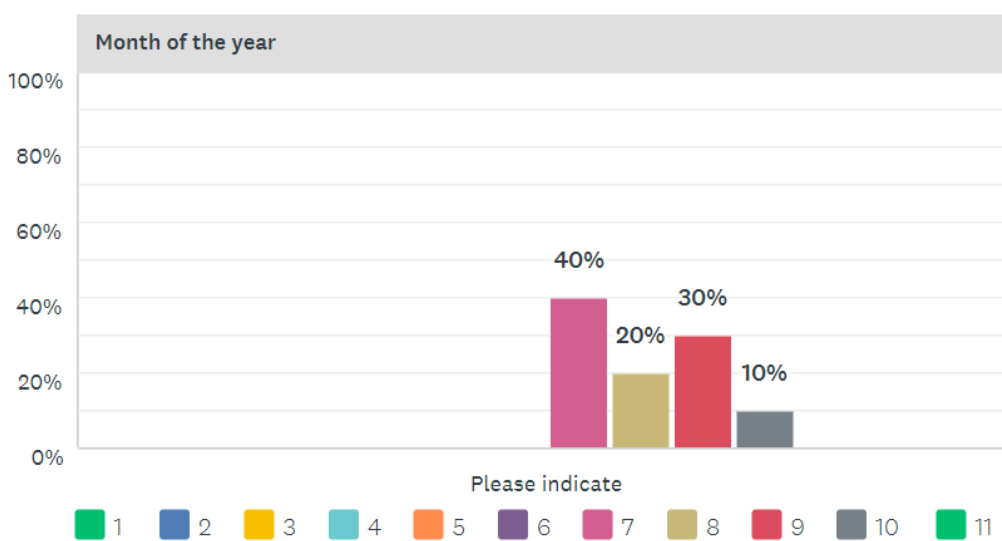


Figure 4 - Month of ethics committee submission

The average time from submission to endorsement from the ethics committee was 5 weeks (SD 2.9), ranging from 1 to 12 (median 4) weeks.

Personal information was anonymized or pseudonymized and security of all data was guaranteed by normalized procedures in 91.7% of cases; the most common scenario was removing from the final database any data that could be used to identify the patients (name, surname, identification and clinical history numbers, etc.) and assigning a new unique study code to each patient.

In three study sites, Finland HUS, Greece and Italy ISS, biological samples were sent outside the study institution, in all cases a specific agreement was signed before the beginning of the study and the procedure was approved by ethics committee.

In four sites - Finland HUS, University of Surrey in the UK, Spain FISABIO and the National Institute for Infectious Diseases "Prof. Dr. Matei Bals", Bucharest, Romania - changes in the ethical submission process have been implemented since the enforcement of the new reform of EU data protection rules (GDPR, Regulation (EU) 2016/679), adding additional notes in the study information leaflet and/or in the informed consent form in particular regarding data processing and privacy risks.

In conclusion, we observed that some differences were present between centers, regarding several procedures, sometimes even within the same country. In particular, most disparities regarded the submission of protocols to ethics committee and the need for informed consent. In fact, in all countries with more than one center included (Finland, Italy, Spain), procedures were not consistent between sites, e.g. with some centers requiring ethics committee approval for each season and others that did not need such approval (this was mainly due to the use of secondary data from routine databases). A specific written informed consent form was also not requested in all centers.

The timing of submission to ethics committee was also quite variable between centers, ranging from July to October. Although all submissions were performed in due time before influenza season, it could be desirable to have all protocols submitted during summer months, so that potential amendment requests could be fulfilled in due time. In fact, changes to the protocol were required from HUS, CIRI (cohort study) and Surrey by the ethics committees, resulting, at least for the Surrey site, in a lower number of subjects contributed to the pooled analysis of the DRIVE project: for this reason, we recommend that all study sites submit the documentation within July, so as not to risk delaying the beginning of the study.

For the next years of the DRIVE project, those sites that will participate again in the study will use the experience gained during previous seasons to avoid some of the possible issues encountered (e.g., changes requested to the protocol and its annexes) that slowed down the ethical submission process. The information gathered in this report and its future updates are of great importance for the DRIVE Project in order to harmonize, as far as possible, the ethical submission process among the various study sites and to assist, if necessary, future sites in the process, avoiding the issues and slowdowns experienced by other sites in the previous seasons.

## Annexes

### Annex 1: Survey to assess ethical submission processes and differences in adapted protocols

*DRIVE (Development of Robust and Innovative Vaccine Effectiveness, <https://www.drive-eu.org>) is a European project under the framework of the Innovative Medicines Initiative (IMI, <https://www.imi.europa.eu/>). The goal of DRIVE is to establish a sustainable platform aiming at assessing brand-specific influenza vaccine effectiveness studies in Europe.*

*This survey targets associate partners, public health institutes and other organizations that perform Influenza Vaccines Effectiveness (IVE) studies in the 2018/19 influenza season. The aim of the survey is to assess differences in the adapted local protocols and the rationale for such differences.*

#### 1. Please provide your contact details

Name

Organization

Country

Position

Address

Email

Telephone

#### 2. Is the influenza vaccine effectiveness (IVE) study conducted by your unit nested into the national influenza surveillance system?

- Yes
- No

#### 3. What are the country-specific regulations that are to be followed to perform IVE studies?

#### 4. Which laws/guidelines apply to the transfer of data to DRIVE?

5. What authorizations/clearances/permissions are required (e.g. from a regional/national data protection officer)? \_\_\_\_\_

6. Which laws/guidelines apply to the rights of the data subject? \_\_\_\_\_

7. How are study subjects explicitly informed about the use of data? If not, why (i.e. arranged through a specific waiver, etc.)?  
\_\_\_\_\_

**8. Is ethics committee approval required for performing IVE studies?**

- Yes
- No

If you answered "Yes", please describe the process briefly.

If you answered "No", please elaborate if needed.

**9. Which ethics committee needs to receive the documentation? In case information on the ethics committee is available in a website, please provide the link here: \_\_\_\_\_****10. Which ethics committee has been consulted?**

- National
- Regional
- Local
- Institutional

**11. Which of these professionals compose the ethics committee?**

- Clinicians
- Psychologists
- Lay persons
- Pharmacologists
- General practitioners
- Paediatricians
- Microbiologists
- Biostatisticians
- Pharmacists
- Experts in legal and insurance matters or coroners
- Experts in bioethics
- Representatives of patient associations
- Other (please specify)

**12. Is informed consent needed?**

- Yes, written consent
- Yes, oral consent
- No

**13. If you answered no to the previous question (12), is a legally valid waiver for informed consent approved by an Institutional Review board?**

- Yes
- No

**14. If you answered yes to the previous question (13), is the approval of waiver for informed consent study-specific or general for vaccine effectiveness surveillance?**

- Study- specific
- General for VE surveillance

**15. What are the documents that need to be submitted to the ethics committee?**

- Study protocol
- Patient information sheet
- Informed consent form
- Informed assent form
- Authorized representative form
- Declaration of sponsorship
- Declaration on conflict of interest
- CV of the principal investigator
- Principal Investigator declaration
- Liability insurance
- Study budget
- Confidentiality agreement from the involved researchers
- Other (please specify)

**16. What was the feedback received from the ethics committees on the protocol used in the 2018/2019 influenza season?**

- Approved
- Not approved
- A revision of the protocol was required (Please specify)\_\_\_\_\_

**17. When do the investigators need to submit the documentation to the ethics committee to start the IVE study at the beginning of the influenza season? Please indicate the week of the year (number) and/or the month (number)**

- Please indicate Week of the year
- Please indicate Month of the year

**18. What are the usual lead time from submission to endorsement from the ethics committee?** Please indicate the number of weeks

**19. Did the study protocol need amendments or administrative changes according to the Ethics Committee?**

- Yes
- No
- If the study protocol needed amendments, please describe which amendments were required\_\_\_\_\_

**20. Is personal information anonymized or pseudonymized and security of all data guaranteed by normalized procedures?**

- Yes
- No
- If you answered yes, could you detail in which way your data is pseudonymized/anonymized?\_\_\_\_\_

**21. Does your study involve sending biological samples outside your institution/abroad?**

- Yes
- No

**22. If you answered yes to the previous question (21), which authorizations / transfer agreements are required to send samples outside?\_\_\_\_\_**

**23. What changes in the ethical submission process have been implemented since the enforcement of the new reform of EU data protection rules (GDPR, Regulation (EU) 2016/679) in May 2018?**

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***Please provide us with the documentation required by the ethical committee for approval of IVE study, including the informed consent form. Documents can be uploaded using the "Choose file" buttons below or sent by email to DRIVE consortium member Miriam Levi (Email: [miriam.levi@uslcentro.toscana.it](mailto:miriam.levi@uslcentro.toscana.it))***

**24. Please upload here the informed consent**

- Only PDF, DOC, DOCX, PNG, JPG, JPEG, GIF files are supported (max 16 MB)

**25. Please upload here the patient information sheet**

- Only PDF, DOC, DOCX, PNG, JPG, JPEG, GIF files are supported (max 16 MB)

**26. Please upload here the study protocol, in English if it is available, otherwise in the local language**

- Only PDF, DOC, DOCX, PNG, JPG, JPEG, GIF files are supported (max 16 MB)

**27. Please upload here the ethics committee approval**

- Only PDF, DOC, DOCX, PNG, JPG, JPEG, GIF files are supported (max 16 MB)

**28. Would it be possible for us to contact you again (or to contact a colleague of yours) in case we need to gather further information?**

- Yes
- No
- In case we can contact a colleague, please provide us with his/her contact details\_\_\_\_\_

**29. Please write in the box below any additional comments you might have**