Blueprint of a framework to rapidly provide scientific evidence on post-marketing vaccination benefits and risks for informed decisions

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List of abbreviations

AE: adverse event

AEFI: adverse event following immunisation

AESI: adverse event of special interest

AF: attributable fraction

BCoDE: Burden of communicable disease in the EU

B/R: Benefit-risk

CDC: Centers for Disease Control and Prevention (USA)

CoC: code of conduct

CPRD: Clinical Practice Research Database

Dx: deliverable x in the ADVANCE project

DALY: disability-adjusted life-year

ECDC: European Centre for Disease Prevention and Control

EFPIA: European Federation of Pharmaceutical Industries and Associations

EHR: Electronic health record

EMA: European Medicines Agency

EMIF: European Medical Information Framework

ICD-9 CM: International Classification of Diseases version 9 Clinical Modifications

ICD-10: International Classification of Diseases version 10

ICPC-2: International Classification of Primary Care Version 2

ID: infectious disease

IMI: Innovative Medicines Initiative

IR: incidence rate

IS: intussusception

IPW: inverse probability weighting

MAH: Marketing Authorisation Holder (≈ Pharmaceutical Company)

MCDA: Multiple-criteria decision analysis

MeSH: Medical Subject Headings

MedDRA: Medical Dictionary for Regulatory Activities

NPHI: National Public Health Institute

NPV: negative predictive value

O/E: observed versus expected

PHI: Public Health Institute

POC: proof of concept

PPC: private-public cooperation

PPP: private-public partnership

PPV: positive predictive value

RCT: randomised controlled trial

RI: Relative incidence

RRE: remote research environment

RVGE: rotavirus gastroenteritis

SE: sensitivity

SP: specificity

SNOMED-CT: Systematized Nomenclature of Medicine - Clinical Terms

TESSy: The European Surveillance System

UMLS: Unified Medical Language System

VE: vaccine effectiveness

VPD: vaccine preventable disease

WP: work package

YLD: years lived with disability

YLL: years of life lost

WHO: World Health Organization

Glossary

AEFI	Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with usage of the vaccine.
Benefit	There are two types of vaccine benefits: the first concerns the protection given to the individual person, the second the change in the overall epidemiology of the disease in the population.
Benefit-risk	The benefit of a vaccination compared to the risk of adverse events. Numerically, it can either be expressed as a fraction: benefit divided by risk, or as a difference: benefit minus risk.
Vaccination coverage	The proportion of a given population (often children at a specific age), that has been vaccinated in a given time period.
Horizon 2020	The seven-year program from European Commission's Directorate General for Research and Innovation.
ICD-X	International Classification of Diseases, version X is a tool to classify all diseases and conditions. It is developed by the World Health Organization and is updated about once per decade.
IMI	The Innovative Medicines Initiative is a joint undertaking between the European Union (represented by the European Commission) and the pharmaceutical industry (represented by the European Federation of Pharmaceutical Industries and Associations – EFPIA). It is reportedly the world's largest public-private partnership in health with an aim to improve the environment for pharmaceutical innovation in Europe by engaging and supporting networks of industrial and academic experts in collaborative research projects.
Implementability	An assessment of how well a developed model could be implemented in reality. In the context of the IMI ADVANCE project, "implementability" has been defined as an assessment, in a structured manner, of the feasibility and usefulness of key project deliverables in terms of meeting the requirements of national and EU/EEA regulatory agencies, national and EU public health agencies, vaccine manufacturers, health care providers and health consumers.
Post-marketing studies	Studies of a vaccine performed after it has been licensed (which can often use much bigger populations than a RCT before licensing).
RCT	'Randomized controlled trial' is a type of study where subjects are randomly assigned to receive either the test drug/vaccine or a standard comparator which can be an inert placebo. The latter group becomes the control group. To avoid potential bias neither the study subjects nor those who administer the drag/vaccine should be aware of assignment.
Regulators	A collective term for the institutions and persons responsible for licensing medical products.

Secondary use	Use of existing health databases for another purpose than that for which they were primarily set up.
Vaccine efficacy/ effectiveness	Efficacy is a measure of cases of disease prevented in a RCT of a vaccine. However, such trials are performed under ideal circumstances. Effectiveness measures how well the vaccine works in a 'real life' program. It also includes indirect effects that are seldom possible to assess in a RCT.

Executive summary

Vaccinations belong to the most successful public health interventions. At the same time, a national vaccination programme is the most extensive medical intervention frequently directed at healthy people – often children. These two facts place responsibility on the public health community and the pharmaceutical companies to assure that vaccines are effective and safe.

The *Accelerated Development of VAccine beNefit-risk Collaboration in Europe* (ADVANCE) is an ongoing European public-private collaboration project that was initiated in 2013 and is scheduled to end in 2018. It is funded by the Innovative Medicines Initiative (IMI), a joint undertaking by the European Union (EU) and European Federation of Pharmaceutical industries and Associations (EFPIA). Forty-seven organisations have participated, including universities, public health institutes, vaccine companies and EU agencies.

The ADVANCE project was created in response to the 2009 A(H1N1) influenza pandemic when European experience highlighted that there were factors limiting the capacity to collect European data on vaccine exposure, safety and effectiveness.

Thus project has had three main objectives:

1. Demonstrate that data from already existing health database (from different countries, with different objectives and in different formats) can be used to assess vaccine coverage, benefits, safety and for a benefit-risk analysis.
2. Create a best practice guidance including governance, code of conduct, quality assurance and communication to describe how partners with different remits and roles can cooperate.
3. Design and test a framework for future studies on vaccines.

The project has been divided into seven work packages, each addressing different aspects of vaccine monitoring framework. The last of these is the development of this Blueprint document. It is based on the technical infrastructure, data sources, methods, code of conduct, rules of governance and workflows in a European network of stakeholders developed and tested by the project.

Following an Introduction, the Blueprint document contains two substantial chapters. The first one is intended to form a manual (“cook book”) for real-life future use of the framework: steps to take, tools to use, links to existing applications and sources – those developed by ADVANCE as well as others. The second contains a discussion on the possible future of the framework – its sustainability after the ADVANCE project has ended.

The manual describes how to use the platform in eleven steps, from activation of the platform to dissemination of results. For several of these steps, the tool or activity to be applied will vary with the actual study question asked. For these steps four different scenarios are used, making it possible for the user to follow one scenario (for example a study of vaccine safety) through the various steps.

The chapter on sustainability describes four different potential models of sustainability, from a loosely connected network of experts and databases, which is activated only when there is a specific question to be studied, to a permanent structure with a small secretariat and a governance structure, which is agreed in advance, independent of any specific study. The last of these models is discussed in some detail.

1. Introduction

1.1 Background

There has long been an awareness that there are factors limiting the capacity to collect European data on vaccine exposure, safety and effectiveness. These factors appear e.g. during the response to the 2009 influenza pandemic A(H1N1), including:

- Lack of rapid access to available data sources or expertise,
- Difficulties in establishing efficient interactions between multiple stakeholders,
- Concerns about possible or actual conflicts of interest (or perceptions thereof), and
- Inadequate public funding to generate the required benefit and risk data and inability of private partners to collaborate with public health institutes to generate the required regulatory data.

As indicated above, there may be problems for some stakeholders to enter into a joint project with other potential stakeholders. One such obstacle is that in most Member States the national public health institutes are the ones holding data on important indicators, such as vaccination coverage, incidence of disease, vaccination status of the cases, etc., but that many of these institutes cannot undertake joint projects with the pharmaceutical industry. Conversely, there may be important data within the Marketing Authorisation Holders (MAHs) which they are not able to share for business and legal reasons.

Another important impetus for launching the project was a signal from the European Medicines Agency (EMA) at the time that they would soon request MAHs to produce brand-specific benefit and risk assessments for the vaccines they are bringing to the market. One should be aware that such post-licensure studies usually require very large study populations to provide dependable estimates of vaccine benefit and of the risk of adverse events. The true benefits can usually not be measured until the vaccine is used widely, and adverse events – even serious ones – may be so rare that they will not be observed in pre-licensing studies. For this reason, a system that collects data from several multiple stakeholders in many Member States may offer more rapid and more relevant results.

Consequently, ADVANCE addressed the feasibility of establishing a public-private collaboration to respond to relevant public health questions regarding the vaccination coverage, benefits and risks of vaccines in a timely and efficient manner with high quality evidence.

The ADVANCE vision was to deliver "*Best evidence at the right time to support decision-making on vaccination in Europe*", and its mission was to establish a prototype of a sustainable and compelling framework for rapid provision of best available scientific evidence on post-marketing vaccination benefits and risks for well informed decisions. Such framework would ensure the provision of a set of tools, data sources, and coordination mechanisms that researchers could use to generate vaccination coverage, benefit, risk, benefit-risk evidence, and other analyses. It would specifically include an operational system and a suite of resources (tools and data sources) that would support vaccine studies, with options according to the type of study and the organisation taking the lead. Depending on the problem to be addressed and the method chosen, different sets of inputs and outputs might be defined within the framework. The framework aims at enabling rather than producing the benefit-risk analysis outputs. Implementation of the Blueprint through undertaking

studies involving actual research teams would need sustainable funding. Options for sustainability of the framework described in this Blueprint are described in detail in chapter 3.

1.2 Structure of the ADVANCE project

The ADVANCE project was divided into seven work packages (WP):

1. Best practice and code of conduct for benefit-risk monitoring of vaccines
2. Creation of synergies for benefit-risk monitoring in Europe
3. Data sources for rapid and integrated benefit-risk monitoring
4. Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit-risk monitoring
5. Proof-of-concept studies of a framework to perform vaccine benefit-risk monitoring
6. Project management and communication
7. Implementability analysis

WP1, 3, 4 and 5 produced White Papers describing the activities and lessons learned and recommendations.

This blueprint document (further called the "Blueprint") builds on the 'White Papers', and on several of the other deliverables of the project. Since the contents of these deliverables are often summarised in the White Papers, the exact source of certain passages or statements from the collective output of the project is usually not referenced.

In the Blueprint reference is frequently made to these deliverables, which are numbered after the work package followed by the number of the deliverable. The abbreviation 'D1.12' for example thus means the 12th deliverable of work package 1. Several of the deliverables are quite extensive, and often contain very useful information, but are too long or detailed to be summarised in the Blueprint, which is why they are inserted for reference. They can all be found on the ADVANCE website: http://www.advance-vaccines.eu/

1.3 Purpose and scope of the Blueprint

This Blueprint describes a framework to realise the vision of the ADVANCE project. The Blueprint defines a framework, within which a range of systems can be implemented according to need. The Blueprint includes a clear description of components, dependencies, workflows, stakeholder involvements and roles, access to the platform/tools developed and tested as part of the project, the entity (entities) in charge of running the platform/tools, and options for financing to ensure sustainability of the proposed solution.

The framework described here should optimally be characterised by, among others: (1) accessibility, (2) acceptability, (3) adaptability, (4) effectiveness, (5) interoperability, (6) reliability, (7) resilience, (8) scalability, (9) simplicity, (10) transparency and (11) sustainability. In the context of the Blueprint this translates into the following key characteristics, i.e. the framework should have:

- operational IT platform
- stable operational and managerial organisational structure and tools
- dedicated trained staff, available centrally and locally
- well-defined and tested processes and rules of interactions between stakeholders
- template documents for each step during evidence generation

- secured base funding
- mechanisms to ensure data access
- mechanisms to ensure sufficient data quality, comparability across different sources and continuous validation of data sources
- data security and privacy assured as per General Data Protection Regulation (GDPR)[1]

The scientific area covered by the Blueprint – vaccination coverage, benefit, risk and benefit-risk assessment conducted throughout the life cycle of vaccines – is quite specific, due to several factors: The benefits and risks of vaccines are perceived and weighed differently, and at different times from other medicinal products as they are often offered prophylactically to healthy individuals, e.g. as part of the national childhood vaccination programmes. Vaccinations thus have major public health implications and, in addition, get a lot of media attention. Hence, the tolerance for risk, even if it is an easily treated adverse event, is very low, as current debate in several EU Member States demonstrates. Stakeholders working in the vaccine area therefore need to monitor relevant data continuously and need to have data easily available for quick decision making and risk management. Other specificities of scientific studies of vaccines include large vaccinated populations, indirect effects of vaccination, multiple stakeholders involved in decisions on vaccination and the differences in time scales over which risks and benefits of vaccination are observed.

In the ADVANCE concept, evidence on vaccine coverage, benefits, and risks may be generated faster through secondary use of existing health care data in Europe. This follows from the realisation that benefit-risk information on a particular vaccine is often needed rapidly, leaving little or no time for specific primary data collection (even if the delay in updating of available databases may in some instances be a limiting factor). This concept was tested by ADVANCE partners who have access to data sources including general practice databases, claims databases, vaccine registries, vaccine trial cohorts and disease surveillance data.. The aim was to test whether the ADVANCE framework could permit the rapid generation of information on benefits, coverage, and risks of vaccines from these data sources both in the characterisation and in the conduct of specific studies. In order to maximally take advantage of these different data, ADVANCE has established a distributed network model comparable to existing networks in the US (Sentinel, Vaccine Safety Datalink) and Canada (the Canadian Immunization Research Network), although differences exist between the different approaches (see chapter 1.4 below for details).

As envisioned, the Blueprint describes a framework that focusses on providing timely evidence on the benefits and risks of vaccines at the request of different stakeholders. These requests/needs could arise under a number of scenarios described in chapter 2.

Under these scenarios, it would be possible to leverage the infrastructure developed by ADVANCE to investigate how the benefits and risks could also be monitored sequentially (cumulatively when data become available) to investigate whether the benefits, risks and composite measures of benefit/risk evolve over time.

The main part of this Blueprint (Chapter 2) is written as a practical guideline for use of the framework. It describes the distinct steps to take when assessing the benefit-risk of vaccines post

[1] https://ec.europa.eu/info/law/law-topic/data-protection/reform_en

marketing. This document also outlines the software tools and contains links to a library of protocols which can be used in benefit-risk studies of vaccines.

In addition to the primary objective to assess benefit-risk, a system that is based on the framework can have other uses. Some examples are: assessing the background rates of events of interest, estimating vaccine effectiveness, estimating coverage, studying vaccine utilization (e.g. identification of missed opportunities for vaccination), studying the burden of vaccine-preventable diseases, etc.

It should be noted that benefit-risk monitoring is – to a large extent – a national activity. Since the values assigned to benefit and risk estimates may differ from country to country, the conclusions from the monitoring may vary in different countries. Framework described in this Blueprint is not meant to replace the national activities but to facilitate conducting similar activities across EU/EEA Member States, using similar methods and tools. It is flexible enough to be used at the national or sub-national level, as needed.

One thing that the framework (at least initially) is not attempting to do is to pick up signals of new adverse event following immunization (AEFIs); the framework is rather intended for use when such a signal has already been observed, and when a more rapid or formal and scientific evaluation is needed. Systems to identify AEFI signals already exist and include spontaneous reporting frameworks, including EudraVigilance[2].

It is important to realise that not all the elements of the described framework have been tested in real world situations to date (e.g. the study governance models), as in ADVANCE no studies were conducted to obtain scientifically valid results – the first proof-of-concept study only looked at the performance of the system that is based on the framework.

With this caveat kept in mind, the Blueprint includes (in relevant text boxes throughout the document) the descriptions of areas for potential improvement. Moreover, only using the framework of the described system and its tools for studies could tell how well they work and where improvements are needed.

1.4 Audience and potential stakeholders of the Blueprint

The primary audience of the Blueprint comprises the future users of the framework, i.e. experts engaging in benefit-risk monitoring of vaccines (or vaccine studies in general) and decision-makers who may either be responsible for commissioning studies (such as public health authorities deciding on vaccination programmes) or requesting them to be performed (such as regulators). Another audience includes policy-makers and others with an interest in the results of benefit-risk monitoring of vaccines (such as the European Academy of Paediatrics) who seek an overview of the framework described in this Blueprint, and what it can deliver. The range of stakeholders in vaccine benefit-risk monitoring in Europe is indicated in Fig. 1.

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp

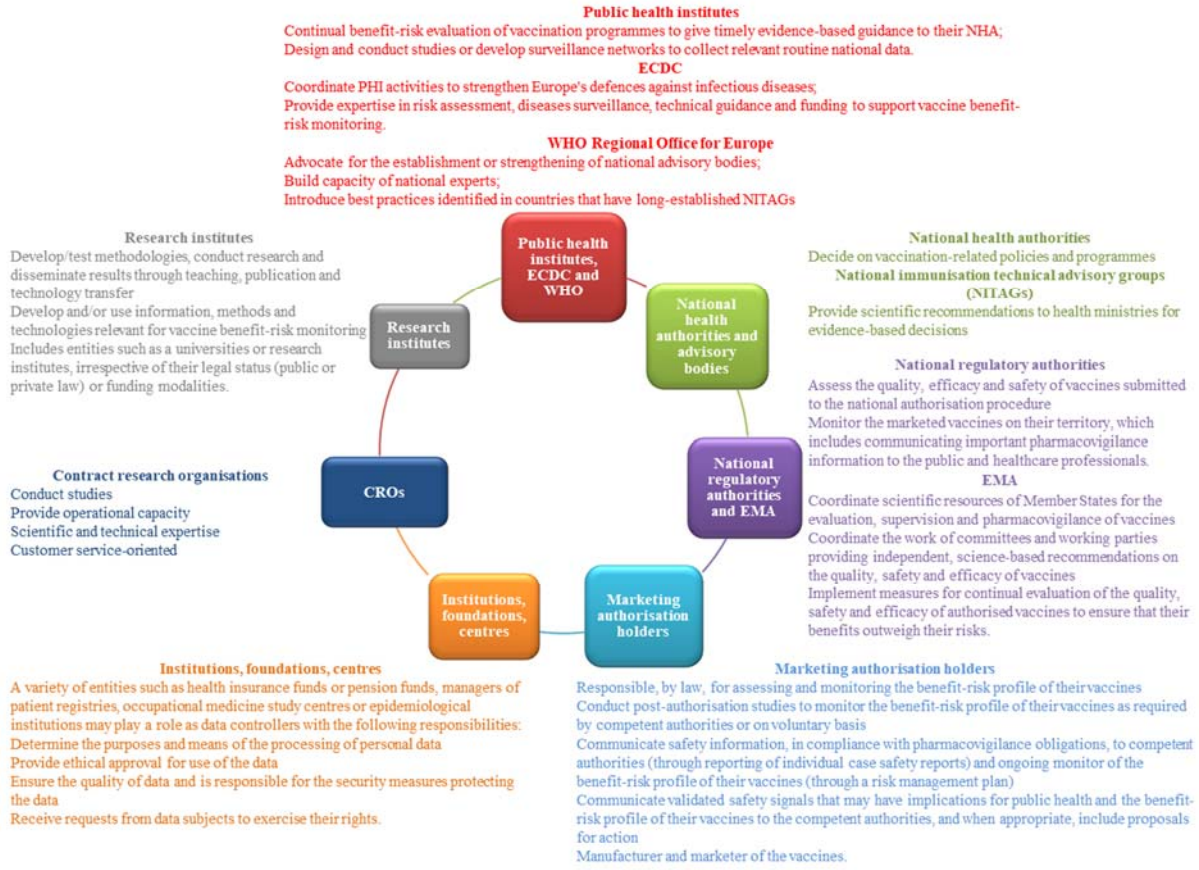

Figure 1. *Key stakeholders in vaccine benefit-risk monitoring in Europe*

1.5 The landscape: existing networks for assessment of vaccines

The Vaccine Safety Datalink[3] (VSD) was started by CDC in 1990. It is a collaborative project between CDC and 8-10 managed care organisations, and has data on around 10 million subjects. It has been used for monitoring of various aspects of vaccines and vaccination programmes, including vaccine safety, effectiveness, coverage, etc. The current estimated annual costs of running the VSD project is around 8 million USD, which is funded by public money. Another similar, but more recent system in the US is PRISM (The Post-Licensure Rapid Immunization Safety Monitoring), a program to actively monitor the safety of vaccines using electronic health records which has data from more than 100 million subjects.

The Canadian Immunization Research Network[4] (CIRN) is a network of over 100 researchers in 40 Canadian institutions that evaluates the safety and impact of vaccines and vaccine programmes. CIRN supports collaborative research among vaccine researchers and stakeholders, trains the next generation of immunisation researchers, and facilitates two-way knowledge exchange between researchers and public health decision-makers. CIRN's priorities are determined by consultation with public health stakeholders, clinicians, and vaccine researchers. CIRN develops and tests methods to

[3] https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html

[4] http://cirnetwork.ca/

assess vaccine safety; assesses how well vaccines are working; evaluates vaccine programmes for uptake; examines strategies to address concerns about vaccination in the public and among clinicians; and can quickly launch research when there are outbreaks or new infectious diseases. CIRN comprises 8 sub-networks: the Clinical Trials Network, Serious Outcomes Surveillance Network, Canadian National Vaccine Safety Network, Special Immunization Clinics Network, Provincial Collaborative Network, Reference Laboratory Network, Modelling and Economics Research Network, and Social Sciences and Humanities Network.

In Europe there are also some examples of networks to address elements of benefit-risk evaluation of vaccines or whole vaccination programmes. One is I-MOVE+ (Integrated Monitoring of Vaccines in Europe), a 26 partner consortium largely of regional and national public health institutes from across EU/EEA Member States. It seeks to develop a sustainable platform of integrated primary and secondary care and laboratory data to evaluate existing and new vaccines.

2. The generic study process

This part of the Blueprint is intended to be a practical guide to using the framework for vaccine studies. It is called 'generic' since it should cover various types of studies, but the intention is that different parts could be picked out to fit the actual study. It describes 11 steps to be taken, not all of which may be needed for every study.

Each step contains practical advice, consisting partly of short descriptions, explanations and hints, partly of references to available material, such as protocols, publications, web sites, etc. The written output of the ADVANCE project is frequently referred to.

The steps of the generic study process are:

Step 1. Activation of the framework
Step 2. Defining the study question
Step 3. Setting up the study team
Step 4. Deciding on the specific study governance
Step 5. Choosing the methods
Step 6. Developing the study protocol and the statistical analysis plan
Step 7. Identifying available data sources
Step 8. Securing ethics and data protection approvals
Step 9. Extraction and transformation of data
Step 10. Data analysis
Step 11. Developing a communication strategy

The steps may differ depending on the study question. We will use four scenarios to describe the process, where each scenario is linked to a specific type of study question. The scenarios are:

a. Benefit-risk monitoring
b. Vaccine benefit assessment
c. Vaccine safety assessment
d. Vaccination coverage monitoring

Step 1. Activation of the framework

Depending on the future development of the ADVANCE platform, and on the model chosen for a sustainable structure (see Chapter 3), the mode of activation may vary. In the 'central hub + platform' model, potential users of the platform would submit a request for proposal in the form of a short study synopsis to the Steering Committee, which would then seek assistance from the Scientific Committee in judging the scientific soundness of the approach described. In case of the use of the framework for a continuous monitoring, it should be constantly active.

Some examples of situations when the framework could be activated are, for the different scenarios:

Benefit-risk monitoring

- When there is a specific issue related to the benefit-risk. The framework could also be used in a continuous way, for example after the inclusion of a new vaccine in a vaccination programme when there is a need to pro-actively monitor (at predefined intervals or in real time) the benefit-risk using e.g. a list of pre-defined adverse events of specific interest.

Vaccine benefit assessment

- To measure vaccine benefits depending on vaccine impact and burden of the vaccine-preventable disease (which may be study questions per se).
- When the benefit of the vaccine is questioned (e.g. mutations of the pathogen, waning immunity, suboptimal effectiveness of a vaccine in some population groups).

Vaccine safety assessment

- Either when there is an expected (from pre-authorisation studies or from experience with similar vaccines) adverse event, or when there is a signal of a new suspected/potential adverse event. In both cases it is often important to know the background rate of the condition in question, either in the presently unvaccinated, or – before the vaccine was introduced – in the entire population.
- Vaccination coverage When there are signs of decreasing vaccination coverage.

Step 2. Defining the study question

The type of question asked will inform which study type and method to choose, how to set up the study team, and which databases could potentially be used. Therefore, stating clearly the scientific question is the initial step in the process of using the framework, after the need for its activation has been identified. Some examples of study questions for the four scenarios are listed below.

Benefit-risk monitoring

- For continuous monitoring of B/R: What is the B/R ratio during the specified period?
- For introduction of a new vaccine: what is the trend in the benefit-risk ratio or benefit-risk difference of a new vaccine monitored at regular intervals following its introduction in a vaccination programme? Does the value of benefit-risk ratio or difference exceed a pre-defined threshold? Does it stay in line with the expectations derived from the clinical development?

Vaccine benefit assessment

- What is the burden of disease prevented by the vaccine?
- For signs of low/decreasing impact: Is there an increase in diagnosed/reported cases of the disease even though coverage remains stable? How is the disease generally diagnosed, and have there been changes in this scheme? Is there a bias in the frequency of taking samples between vaccinated and unvaccinated – and how is this avoided?

Vaccine safety assessment

- Is there a statistically significant link between vaccination and the AEFI (regardless of causation)? What is the time distribution between vaccination and appearance of the suspect AEFI? Does incidence of the suspect AEFI vary by age? By gender? By vaccine brand?
- The incidence of the disease that the vaccine is directed at before vaccine introduction (background rates) to support observed/expected analyses.
- A potential AEFI has been observed, and we want to use existing health databases to find out how common this condition is in the general (unvaccinated) population, or was before the vaccine was introduced.

Vaccination coverage monitoring

- For signs of decreasing coverage: Has the country introduced a new way of collecting coverage data? Have dynamic effects been considered? Is the decrease statistically significant? Is there a bias in the collection of data, which may be changing over time?

Step 3. Setting up the study team

(These issues are discussed in detail in deliverables D5.3 and 5.6, to be found on the ADVANCE website: http://www.advance-vaccines.eu/)

This step applies in the same form to the four identified scenarios. There are two conditions to take into account when setting up the study team. One is technical: which kinds of expertise and experience are needed for this kind of study? Which databases may be useful and available? (see Step 7 below). The other concerns study governance: which are the potential partners, and what are the rules for their cooperation? Where would the funding come from?

Studies under one of the four scenarios may be initiated and conducted for several reasons, such as to fulfil regulatory requirements, to respond rapidly to a safety signal, to generate on-going information on the vaccine benefit-risk profile or to inform future vaccine research and development. At this stage, the full spectrum of possible future 'requesters' is difficult to envisage.

When selecting members for such studies, one should be aware of different challenges:

- The need to assess data from different sources, e.g., electronic health records, vaccination registries, disease surveillance systems, media reports, social media reports, and laboratory databases. Competence on working with such sources needs to be secured in the team.
- The need for the team to respond rapidly when immediate action and communication may be key to protecting public health and public trust, for example, in the event of disease outbreaks or vaccine safety concerns.
- The need to have access to data from large populations in case of rare adverse events and take into account demographic and geographic factors when estimating the benefits and risks of vaccines, which may require data collection from databases – and participation by database owners – from several countries.

One specific group of potential members for the team are the database owners/custodians, who should always be included. Their knowledge of the strengths and weaknesses of their databases is an asset for the study.

Step 4. Deciding on the specific study governance

It is clear that many studies will require participation from several stakeholders and that timely projects on vaccine benefits, risks and coverage may therefore only be possible – or may be facilitated significantly – if there are established collaborations between key stakeholders involved in data collection, management and assessment for vaccine exposure, safety and effectiveness. This implies that for most study teams governance structures will have to be set up, tailored to the study question and accompanied by codes of conduct.

One of the main issues during the ADVANCE project has been that different stakeholders may have different possibilities to take part in multi-partner projects, and that a governance model that suits one stakeholder may not fit another.

There are three types of possible cooperation in a vaccine study:

i. A private-private cooperation (for example by two or more vaccine manufacturers)
ii. A public-public cooperation (for example between two or more public health institutes)
iii. A public-private cooperation (for example between a public health institute and a vaccine manufacturer)

One of the most important restrictions is to what extent National Public Health Institutes (PHIs) are able to cooperate with representatives of the vaccine manufacturers in studies to asses, for example, effectiveness or potential adverse events. The specific concerns for PHIs include risks relating to the perception of their scientific integrity and independence if they collaborate with industry. They may fear loss of public trust, which may potentially have an impact on their national vaccination programmes or beyond. However, for other EU PHIs, a public-private cooperation is distinctly possible.

These differences in remit imply that one single governance model will not be possible to attain for studies involving all potential stakeholders. The best solution has been to design a generic governance model, which could be adapted to the particular situation. The ADVANCE generic study model is depicted in Figure 2.

It should be noted that the word 'governance' has two slightly different connotations in the ADVANCE project. The one used here – 'study governance' – refers to the structure/methods for running a specific study on vaccines. In Chapter 3, the term 'platform governance' signifies the structure for overseeing and running the potential future platform emanating from the ADVANCE project – a platform which may in itself be used for several different studies. The model described in Fig. 2 refers to the specific study governance.

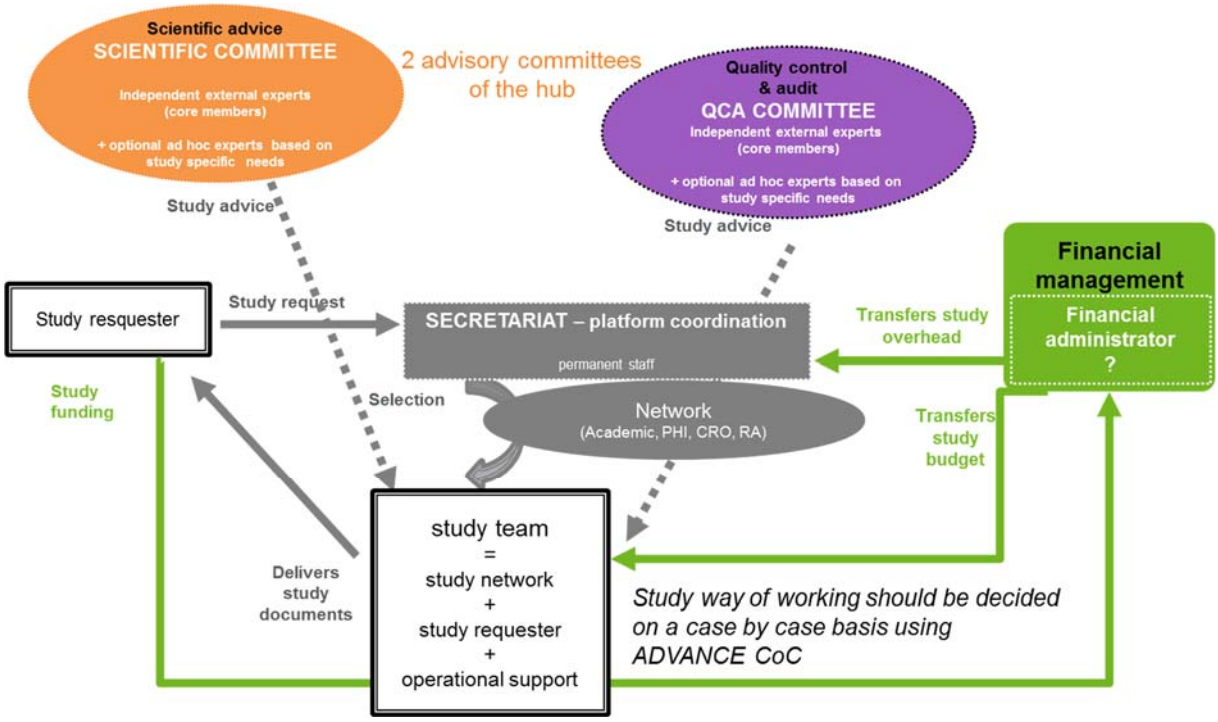

Figure 2. *A generic study governance model*

Overall, there are five different governance functions:

1. Decision-making
2. Scientific advisory
3. Quality control and audit
4. Implementation and management
5. Financial management

It is important to realize that financial management should be handled separately from study management, scientific discussions, quality and audits. Financial conflict is one of key factors for public perception, trust and potential conflict of interest.

When selecting members of the governance group for a study, ADVANCE has elaborated the following list of questions. Most of them apply to all possible cooperation options (i through iii):

1. What are the objectives and goals of the project?
2. What are the added value / constraints for a collaborative project?
3. What are the best processes for the selection of partner organisations for the specific project? The selection of the partner organisations could be managed through different processes (e.g., selection from a list of potential partners, open call) under the responsibility of various entities (e.g., funders, committees, external organisations).
4. How can the generic governance model be adapted to suit the specific project context and objectives?
5. How should the roles and responsibilities be defined?
6. How should committees for the PPC governance structure be established?
7. How should representatives of partner organisation be nominated?
8. What external expertise is required and how should external experts be selected?
9. What legal considerations should be taken into account for the collaborative project?
10. How should conflicts of interest be managed?
11. What project communication plans will be needed?
12. What should be included in the project contract?

One can assume that members of the ADVANCE consortium will continue to be involved in any future use of the platform, but also that new members will want to access it.

Authorship of publications

Early in the process of setting up the study, the team needs to agree on who will take part in the scientific communication of possible results, according to international guidelines (e.g. those issued by the International Committee of Medical Journal Editors – ICMJE[5]).

[5] http://www.icmje.org/

Code of Conduct

For several of the possible governance structures a Code of Conduct for the partners will be needed. The published ADVANCE Code of Conduct includes 45 recommendations on 8 topics:

- Scientific integrity
- Transparency
- Conflicts of interest
- Study protocol
- Study report
- Subject privacy
- Sharing of study data
- Research contract

The full list can be found in Annex A. The document distinguishes two levels of recommendations: 28 are considered critical and should be applied in all studies (‘‘must”) and 17 should be considered for all studies but may be less critical for the study governance (‘‘should”). In case of public health crisis requiring faster conduct of a study, investigators may focus on recommendations with a ‘‘must”.

The Code of Conduct was tested in the Proof of Concept study on pertussis vaccines and found workable.

Other available codes of conduct useful in studies of benefit-risk of vaccination include e.g. the ENCePP code of conduct[6].

Step 5. Choosing the methods

Scientific method(s) depend on the research question. In the following subchapters we outline some general practical steps involved in methodology of vaccine studies. The detailed methods available are well described in three deliverables from Work Package 4 of the ADVANCE project:

D4.1 on methods to estimate coverage and measure benefits

D4.2 on safety and signal detection

D4.3 on how to compare benefit and risk

These three reports can be found on the ADVANCE website (http://www.advance-vaccines.eu/) and readily be used as handbooks when designing a study.

In addition to these reports, D4.4 contains a thorough discussion of problems commonly encountered in vaccine epidemiology, such as misclassification, heterogeneity, case ascertainment, to mention a few. This deliverable also covers several developed solutions and tools.

[6] http://www.encepp.eu/code_of_conduct/

The available choices of methods for the different scenarios are listed below.

Benefit-risk monitoring

It is essential to understand that pharmaceutical benefit-risk assessment involves not only accurate, quantitative measurements of benefits and risks, but also – unavoidably – value judgments about the relative importance of the various benefits and risks.

Most benefit-risk methodologies available to date have been developed to assess the benefit-risk balance of (therapeutic) drugs or devices, and relatively little has been published about benefit-risk monitoring of vaccines. An overview of such methods is available in the Deliverable 4.3, and more extensively in the IMI PROTECT project[7]. They can be categorized into:

1. Descriptive or semi-quantitative frameworks (see discussion on Multi-Criteria Decision Analysis - MCDA below, and the description of the DECIDE instrument[8])
2. Benefit-risk measures
3. Composite health measures (see discussion on DALY methods below)
4. Quantitative benefit-risk frameworks
5. Modelling approaches commonly used in Health Technology Assessment
6. Parameter estimation and uncertainty
7. Preference elicitation techniques

In particular, two groups of methods have been elaborated within the ADVANCE project and include the descriptive/semi-quantitative frameworks using multi-criteria decision analysis (MCDA)–based methods on the one hand, and composite health measures–based approaches, especially using disability-adjusted life years (DALYs) on the other.

a) MCDA. The descriptive/semi-quantitative frameworks have been developed within the PhRMA Benefit-Risk Action Team (BRAT[9]) and the PROTECT project's PrOACT-URL (Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, and Linked decisions) frameworks and are currently the most commonly used ones. ADVANCE recommends using (and potentially modifying) these frameworks for the benefit-risk assessment of vaccines.

MCDA includes the following general steps:

- Context: establish the decision context and describe the perspective
- Alternatives: identify the alternatives to be appraised
- Criteria: identify and define the benefit and risk criteria and organize in a value tree
- Scoring: criteria measurements, assess the performance of each alternative against the criteria (so called "effects table")
- Value functions: transform the scores to preferences on the 0-1 scale
- Weighting: assign a weight to each criterion based on preferences of various health states elicited from a relevant panel.
- Results: calculate results and provide graphs

[7] http://www.imi-protect.eu/

[8] http://www.decide-collaboration.eu/

[9] http://www.cirs-brat.org/

- Sensitivity analysis: explore the effects of uncertainty on the benefit-risk balance. Here, Monte Carlo (MC) simulation can be performed to investigate the impact on the benefit-risk balance of: (1) statistical uncertainty in the benefit and risk estimates (uncertainty analyses), (2) differences in preference, and (3) subjective model choices (e.g. different case definitions). Additional sensitivity analyses can be performed to identify the pivotal benefit and risk outcomes.

An example protocol of MCDA applied to a concrete benefit-risk evaluation is the ADVANCE proof-of-concept study 1 benefit-risk protocol[10]. This protocol can be adapted to a given vaccine-study question.

In addition to ad-hoc benefit-risk analysis of a vaccine, near-real time monitoring approach of vaccine coverage, pre-specified health benefits and risks of vaccines has been developed within the ADVANCE project[11],[12].

b) DECIDE. A further general recommendation when working with descriptive or semi-quantitative frameworks is to investigate the use of an evidence grading methodology, such as the GRADE[13] system for post-authorisation benefit-risk assessment because it typically involves the integration of various sources of information of different quality (e.g. clinical trials, different types of databases, epidemiological studies and infectious disease modelling). An adaption of GRADE has been developed in a H2020 project called DECIDE[14], which has been used by the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute– a committee that advises on the introduction of new vaccines in the German national programme.

c) Composite measures of population health e.g. DALY-based methods. Another approach is to use DALYs for benefit-risk assessment of vaccines and vaccination programmes. The idea is to compare the burden of disease averted by the vaccine to the burden of disease caused by adverse events, and by using DALYs the benefit and the risk can be put on a common, quantitative scale.

The DALY is one of the most commonly-used summary measures of population health, and is typically applied to compare the relative impact of diseases in a population. The DALY combines the years lived with disability for a health state (i.e. living with a condition, disease, disability, or injury) with the years of life lost due to premature mortality; thus, time is the metric for both morbidity and mortality. One DALY is equivalent to one lost year of healthy life.

DALYs have been used to estimate the Burden of Communicable Diseases in Europe (BCoDE project of ECDC) and to estimate the cost-effectiveness of vaccination programmes (guide of the World Health Organisation[15]). The validity of DALYs is sometimes questioned but these concerns are related to the use of DALYs to evaluate life-extending interventions and are not related to vaccination.

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[10] http://www.encepp.eu/encepp/openAttachment/studyResult/21719;jsessionid=892SR8lOSvk5nW-GUCTgjEkbYRMmG3dajKzmAhDFEKslYlVuj7N9!-53086593

[11] http://apps.p-95.com/BRMonitor/

[12] https://link.springer.com/article/10.1007%2Fs40264-018-0658-y

[13] http://www.gradeworkinggroup.org/

[14] http://www.decide-collaboration.eu/

[15]http://apps.who.int/iris/bitstream/handle/10665/69981/WHO_IVB_08.14_eng.pdf;jsessionid=900E181D8DDCE99501E5AF8FAFA681BE?sequence=1

A complete toolkit to calculate burden of communicable diseases (including vaccine-preventable diseases) is available at ECDC[16] website.

The steps of estimation of DALYs lost due to vaccine-preventable diseases, used in the ECDC toolkit are outlined in Figure 3.

Figure 3. *Steps to estimate the DALYs lost due to vaccine-preventable diseases (from the ECDC 'Burden of Communicable Diseases in Europe' project)*

A similar methodology can be used to estimate the burden of AEFIs. The detailed methodology is available in Chapter 9 of Deliverable 4.3 of Work Package 4, and also in the published paper[17].

First the candidate adverse events have to be selected. Only candidate AEs for which an incidence rate could potentially be determined from electronic health records should be included. Note that very mild local reactions will most often not be included.

Next, the incidence of such events in the absence of a vaccine needs to be determined or estimated – in order to obtain a background rate. It can be provided by literature searches, or from electronic health records.

Subsequently, the incidence of the event in people who have been vaccinated has to be determined. The same sources are used as those for the assessment of the background rate. Publications providing estimates of the relative risk (or the absolute risk, defined as cases per vaccine dose) for the identified vaccine-event pairs can be retrieved via PubMed searches. Sometimes, conducting a meta-analysis of published risks for each vaccine-event pair might be needed.

[16] https://ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys

[17] McDonald SA, Nijsten D, Bollaerts K, Bauwens J, Praet N, van der Sande M, Bauchau V, de Smedt T, Sturkenboom M, Hahné S. Methodology for computing the burden of disease of adverse events following immunization. PharmacoepidemiolDrug Saf. 2018 Mar 24. doi: 10.1002/pds.4419

The vaccination-associated disease burden of each adverse event of interest can be estimated using the DALY measure, which is the sum of years of life lost to premature mortality (YLL) and years of life lived with disability (YLD):

DALY = YLL + YLD

YLL = No. deaths x life expectancy at age of death

YLD = No. events x disability weight x duration

Assigning figures to the disability weights is usually the most problematic part of the method, since it builds on values and preferences. Nevertheless, the weights try to encode the severity of the health outcome, and can be obtained from professional or lay populations using a variety of preference elicitation methods; the current Global Burden of Disease approach is to use general public survey respondents. The disability weight runs on a scale from 0 (perfect health) to 1 (death). If not available from existing databases or from literature, then weights from proxy health outcomes need to be assigned, ideally through consultation with experts with appropriate medical knowledge. Disability durations are typically determined from literature review and/or clinical expert knowledge. For a more complicated set of outcomes, a disease tree may have to be constructed.

The single most important outcome required for computing the health burden of adverse events is vaccination-attributable event incidence. 'Vaccination-attributable' does not make a strong assumption that the observed adverse event has a causal relationship with the vaccine itself, but merely that the event is associated with administration of the vaccine. 'Attributable' refers to the extent to which the event incidence is associated with vaccination, adjusting for the background incidence in the population.

There is a discussion of various other methods that could be used for benefit-risk studies on pp. 68-71 of Deliverable 4.3 of Work Package 4[18]. However, the list is to some extent theoretical, as several of the methods have not been tested 'live' in the ADVANCE project.

Recommendations for future developments

The MCDA approach was selected among other methods by the ADVANCE project. A comparison of other methods and metrics with an indication of how these might affect the results would help to make the choice of method more transparent.

Criteria are needed for cases or situations where the different methods would be applicable and useful (and where not). Relevant factors include timeliness and the time horizon of benefits and risks.

[18] http://www.advance-vaccines.eu/

Vaccine benefit assessment

Vaccine effectiveness

The benefit of a vaccination programme – the vaccine effectiveness – is measured as the number of infections prevented by the vaccine. Given as a percentage it is the difference of incidence of disease between the unvaccinated and the vaccinated, divided by incidence in the unvaccinated.

Crucial for this value are:

- The correct diagnostic methods to separate cases of disease from the non-cases (i.e. does the case really suffer from the disease that the vaccine is supposed to prevent?)
- The correct classification of vaccination status in all cases and non-cases (i.e. was the subject vaccinated or not?)

For the first condition, there are computerised databases in most EU countries: the registers of notified cases of a number of infectious diseases set up for surveillance by the National Public Health Institutes. Increasingly, these registers are also becoming linked to computerised laboratory systems, which gives a high specificity for the diagnosis. However, all cases are not notified with a personal identifier for all diseases and in all countries. The issue of defining a disease case goes beyond laboratory confirmation and is related to the way the practitioners clinically diagnose the condition, taking into account the clinical presentation and severity of disease.

Also, obligatory comprehensive notification generally does not exist for some of the diseases where a vaccination has been or may be introduced (e.g. RSV, influenza).

For the second condition, the registers of notified diseases are less useful. Even if the computerised forms in many countries ask for vaccination status, this is often not filled in – and also, the patient may not remember or know.

The ideal situation is thus one where the register of vaccinated persons can directly be linked to the register of cases of disease.

To assist researchers undertaking vaccine effectiveness studies using electronic health databases, a simulation tool has been developed in ADVANCE to explore the impact of differential and non-differential exposure- and outcome misclassification on estimates of vaccine effectiveness[19]. Another tool was designed to derive prevalence estimates of events of interest and validity indices (sensitivity, specificity, positive and negative predictive values) starting from the observed prevalence and two other parameters (either validity indices or the true prevalence)[20].

Impact of the vaccination programme

Another way to estimate the effect of a vaccination programme is to compare the overall incidence after the programme has been launched to the prior incidence – the baseline. This method also requires good surveillance data with high sensitivity (identifying all the cases) and specificity (certain diagnosis), and thus builds on good surveillance registers as well as laboratory confirmation. Of course, as with all surveillance systems, one must be careful to exclude other possible reasons for an apparent change in incidence, such as new laboratory methods, changing disease awareness in the

[19] http://apps.p-95.com/VEMisclassification/

[20] http://apps.p-95.com/Interr/

population and among healthcare providers, etc. This approach could also be confounded by temporal disease patterns of disease incidence.

When using electronic databases with medical diagnoses, it is often unclear whether they can be attributed to the vaccine preventable diseases in question (the use of 'influenza-like illness' as a proxy for influenza infection is one good example). Public health surveillance data can be used to define calendar periods of pathogen circulation which can help to attribute diagnoses recorded during these periods to a specific pathogen.

Direct vs indirect effect

Several vaccines do not only protect against disease, but also decrease the infectivity of cases (the vaccine may, for example, prevent carriage of certain bacteria). Vaccinating an individual does thus not only protects the vaccinee, but also people around him/her. This is called the 'indirect effect'. Including indirect effects in the estimation of benefit-risk of vaccines would allow for a more comprehensive assessment of the impact of vaccination. However, the indirect effect is usually not assessed in randomised controlled trials (RCTs) of new vaccines, since the number of vaccinated is too small to have any effect at the population level. It is not until after authorisation, with a wide use of the vaccine, that the benefit in the form of indirect effect can be observed. It can also be modelled in mathematical modelling studies.

Milder disease

A less tangible benefit is the instance where a vaccine may not protect totally against disease, but where the disease is milder in a vaccinated person. This effect is very difficult to quantify.

Again, for future studies on benefits, computerised databases of vaccinations linked to the population register should be used, ideally covering the entire population of a country.

Example study protocols for vaccine effectiveness studies

Some example protocols that can be used to study the effectiveness (or impact) of vaccines using electronic health records are available and can be adapted to a given scenario. For example, tested template protocols for investigation of influenza vaccine effectiveness are available on ECDC website[21]. They can be adapted to study effectiveness of other vaccines.

Vaccine safety assessment

Rare adverse events to a vaccine may often not be detected until post authorisation, when the vaccine is given under real-life conditions to large groups of people, which underlines the need for systems such as the one outlined here in the Blueprint.

There are two basic situations regarding (suspected) adverse events following immunisation:

[21]https://ecdc.europa.eu/en/publications-data/protocols-cohort-database-studies-measure-influenza-vaccine-effectiveness-eu-and

1. Any change over time in the frequency of already known adverse events;
2. A signal that a so far unknown AEFI is suspected to be linked to a vaccine.

Both situations require accurate population-based registers of health outcomes that may be adverse events linked to a register of vaccinations, since then any existing connection between the event and the vaccine can be assessed.

For rapid assessments, frequency of updating of health databases is of crucial importance, but with more and more health systems applying e-health methods for clinical care, with computerised registers that are automatically updated in real time, this situation is changing. Even so, it should be noted that a proper investigation of an AEFI most often requires a clinical assessment of each case, something that cannot be done in registers.

Some of the epidemiological methods to study safety are:

- Variants of cohort studies (including retrospective cohort studies with the use of risk intervals)
- Variants of case-control studies (including nested case-control studies, case-cohort studies, etc.)
- So called “Self-controlled designs” (including self-controlled case series method, case-crossover method, and their variants)
- Sequential designs (including methods based on sequential probability ratio test)

Vaccination coverage monitoring

The overview concluded that there is currently no standardised method to estimate or report vaccine coverage in Europe. Three estimation methods are used; the administrative method, the survey method, and investigation of computerised records. Detailed description of these methods is available from WHO and in the study of Lopalco and Carrillo Santisteve[22].

The administrative method calculates coverage of a vaccine by dividing the number of doses sold, distributed or administered by the total size of the target population. The calculation is done for certain age groups (e.g. 12 or 24 months), and will miss vaccinations performed after the age recommended in a national programme.

Survey methods are based on questioning subjects about their vaccination history and status using various sampling schemes and data collection methods (direct or telephone interviewing, mailed or online questionnaires, etc.). They are generally expensive, and suffer from several methodological problems.

However, a number of EU countries already have or are developing computerised vaccination registers (also known as immunisation information registers). When both timeliness and vaccine exposure should be taken into account we recommend to use these registers to identify the optimal time for vaccination coverage estimation for each vaccine dose across countries.

[22] http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(14)60169-5/pdf

In the first Proof of Concept study performed by the ADVANCE project, it was shown that similar results for coverage estimation could be attained through an innovative use of already existing electronic healthcare registers. Data from several such databases having different primary objectives were collected and transformed into one single data set. This required new semantic and ontological tool for harmonisation[23], a web applications which allows: 1) the analysis of individual vaccine descriptors, 2) the selection of vaccine codes based on their defining properties and 3) the alignment of any pair of user-provided vaccine coding systems.

Specifically designed vaccine registers as well as such electronic healthcare registers in principle allow continuous vaccine coverage estimation that is not bound to a specific age in months. This is critically dependent on the frequency of updating. As the child's age in months will be available at time of vaccination, Kaplan-Meier curves or other statistical tools can be used to estimate the optimal age to measure vaccination coverage for each vaccine dose across countries when both timeliness and vaccine exposure should be taken into account. The identified optimal age to estimate vaccine coverage should be compared with the country-specific immunisation schedules available from ECDC webpage[24].

Such registers allow in principle timely monitoring at a relatively low cost and often cover large geographical areas. They could also provide coverage information needed for rapid assessment of new safety or vaccine effectiveness concerns. However, the populations captured in these registers may be dynamic, when members move in and out the population over time (i.e. transient membership) for example due to relocation or switch between general practices. This may result in incomplete follow-up, hampering the accurate estimation of vaccination coverage. Incomplete follow-up could lead to an underestimation of the vaccination coverage as vaccines administered outside the follow-up period would not always be recorded.

Nevertheless, for future studies on coverage, computerized databases of vaccinations linked to the population register should be used, ideally covering the entire population of a country.

Description of existing immunization information systems in the EU/EEA countries can be found in comprehensive ECDC report[25].

Step 6. Developing study protocol and statistical analysis plan

ADVANCE has shown that collaboration and commitment across different stakeholders were integral at each of the key steps: study scoping (i.e. defining the research question)/ outline, selection of study teams, protocol writing, analysis and reporting. To be prepared for the future, the project used the available protocol templates and methods standards, and the proof of concept (POC) protocols were subsequently registered in the EU PAS Register hosted by ENCePP.

Examples of already existing protocols for the different scenarios are listed below.

[23] https://euadr.erasmusmc.nl/VaccO/#!/

[24] http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

[25] https://ecdc.europa.eu/sites/portal/files/documents/immunisation-systems.pdf

Benefit-risk monitoring

ADVANCE POC I benefit-risk pillar protocol – testing new approaches to monitoring benefit/risk with pertussis vaccines as test case: benefit-risk analysis of pertussis vaccines in pre-school children comparing whole-cell and acellular formulations in the post-marketing setting[26].

Vaccine benefit assessment

ADVANCE POC I benefit pillar protocol - Testing new approaches to monitoring benefit/risk with pertussis vaccines as test case: Incidence rates of pertussis and pertussis related outcomes of whole-cell pertussis and acellular pertussis vaccines in pre-school children[27].

Vaccine safety assessment

ADVANCE POC I risk pillar protocol - Testing new approaches to monitoring benefit/risk with pertussis vaccines as test case: Incidence rates of safety outcomes of whole-cell pertussis and acellular pertussis vaccines in pre-school children[28].

Vaccination coverage monitoring

ADVANCE POC I coverage pillar protocol - Testing new approaches to monitoring benefit/risk with pertussis vaccines as test case. Coverage rates of acellular and whole-cell pertussis-containing vaccines in preschool children[29].

Step 7. Identifying available data sources

Several general types of data sources can be used for vaccine studies of the kind described in this Blueprint. Due to the accelerated nature of the analyses described here, the primary type of data are electronic records of various sorts. Most of the databases used or suggested by ADVANCE are not created for studies of vaccine benefit-risk. They are rather intended to have a clinical use, to perform surveillance of infectious diseases or have administrative purposes. One of the successes of the project has thus been to show that such databases can also be used for research on vaccine benefits and risks – what is called 'secondary use of data'. In addition, public health surveillance data can also be utilised for analyses described in the Blueprint.

When planning a study, we suggest the following steps to identify available / suitable databases:

- First, consider using databases which were used in the ADVANCE project Proof of Concept studies. More detailed information can be obtained from the results of the ADVANCE AIRR (ADVANCE International Research Readiness) survey available at the EMIF web site[30]. A guide how to access the ADVANCE Web Catalogue through the EMIF site can be found in deliverable D3.4: Catalogue and meta profiles of data sources for vaccine benefit-risk monitoring (ADVANCE Consortium Database[31]).

[26] http://www.encepp.eu/encepp/viewResource.htm?id=21729

[27] http://www.encepp.eu/encepp/viewResource.htm?id=21757

[28] http://www.encepp.eu/encepp/viewResource.htm?id=21721

[29] http://www.encepp.eu/encepp/viewResource.htm?id=21742

[30] http://www.emif-catalogue.eu

[31] http://www.advance-vaccines.eu/?page=publications&id=DELIVERABLES

- If needed, more suitable databases can be identified by a search of a comprehensive existing database catalogue, e.g. the ENCePP database catalogue[32].

Another potentially useful database is The European Surveillance System (TESSy[33], see below). Many databases and registries in Northern European countries (for example for cancer or pregnancy outcome) are not listed in the above libraries, but are usually available to external users.

If the search of a general database catalogue does not provide sufficient information on the characteristics of selected databases, "fingerprinting" scripts (see below) can be run to generate such information.

7.1 'Fingerprinting' of databases

In computer science, fingerprinting is a procedure that maps large data sources to short strings of bits which become their unique identifiers. In the context of ADVANCE, fingerprinting has been defined as a procedure when a new, potentially useful database is being investigated to find out what data are actually available by real data extraction. There are four steps in the procedure:

1. Stepwise conversion of specific required study data into a simple common data model;
2. Describing the data quantitatively using a common script and visualisation;
3. Iterative harmonisation and verification of data extraction steps across the databases: mapping of codes and terms to allow for specific data to be integrated into a common data model;
4. Benchmarking of data extracted against available external sources of information.

In this process, the full involvement of the database custodians in data extraction and interpretation of data is needed to provide the necessary specific knowledge of the data source. They transform their local data into common input files, and these input files are processed locally (e.g. by a specific R script or by Jerboa software tool[34]). Fingerprinting output can then be checked against other available sources to ascertain the representativeness and completeness of the data in the database.

The main data to be fingerprinted are: population, vaccination/vaccine, and outcome/event. For the two latter there is usually a problem with different coding in different database systems and countries. For outcome data, the problem can partially be addressed by the use of the application called CodeMapper[35]. For vaccines, the application called VaccO can be used[36].

7.2 Using public health surveillance databases

At the EU level the main database for public health surveillance of communicable diseases is the European Surveillance System (TESSy). It is a flexible metadata-driven system for collection, validation, cleaning, analysis and dissemination of data for public health action. All European Union Member States and EEA countries report to the system their available data on around 50 communicable diseases described in Decision No 2119/98/EC. The results of TESSy data analyses

[32] http://www.encepp.eu/encepp/resourcesDatabase.jsp

[33] https://ecdc.europa.eu/en/publications-data/european-surveillance-system-tessy

[34] https://www.ncbi.nlm.nih.gov/pubmed/21182150

[35] Becker BFH, Avillach P, Romio S, et al. CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiol Drug Saf. 2017;1-8. https://doi.org/10.1002/pds.4245

[36] https://euadr.erasmusmc.nl/VaccO

(e.g. those shown in the ECDC Surveillance Atlas of Infectious Diseases[37]), should be interpreted carefully, among others due to differences between the national surveillance systems. Within the framework described in this Blueprint, public health surveillance data can be used for several purposes:

- To define periods of predominating circulation of some pathogens, which can be used to attribute diagnostic codes from electronic patient records to concrete diseases (e.g. to attribute electronic codes for respiratory conditions to respiratory pathogens, e.g. influenza.
- To track trends in disease incidence against use/coverage of vaccines.
- As inputs for disease modelling tools e.g. the ECDC Burden of Disease (BCoDE) Toolkit (to estimate the burden of vaccine-preventable diseases). Procedures regulating access to and use of the TESSy data are described in detail under this link[38].

7.3 Databases with linked epidemiological and microbiological information

More and more national surveillance systems now have a direct link between notified cases and the corresponding microbiological test result. This increases both sensitivity and specificity in assigning a patient to the 'case' or 'non-case' group. Molecular and geno-typing will further increase the discriminating power of the microbiological data.

Recommendations for future developments

The added value of building a new catalogue of databases, as compared to relying on existing catalogues (such as ENCePP Resources Database) should be explored – also with regards to the maintenance costs.

Data-rich datasets should be developed to a state of pre-study readiness where the platform can quickly respond to calls/requests.

Participating databases may have to be provided with an indemnity depending on the time spent conducting the feasibility assessment and data submission and, therefore this may have a budget implication.

Step 8. Securing ethics and data protection approvals

The implications of the EU GDPR (General Data Protection Regulation) for future vaccine benefit-risk studies include an expanded territorial scope; mandatory data protection and/or privacy impact assessments (DPIAs/PIAs); requirement for a data processing audit trail; enhanced individual rights; the mandatory appointment of a data protection officer (DPO); increased accountability of data controllers and processors; and new data protection by design and by default. This will require that data protection should be designed into the procedures for data processing and management (including physical and technical safeguards, privacy enhancing technologies, minimisation of

[37] https://ecdc.europa.eu/en/surveillance-atlas-infectious-diseases

[38] https://ecdc.europa.eu/en/publications-data/european-surveillance-system-tessy

processing principle). The 2018 EU GDPR also requires that DPIAs/PIAs are completed and that data processors prove their compliance with the new legislation before processing activities that involve personal sensitive data can start.

A privacy and ethics guidance (PE-tool) was developed and used in the first ADVANCE proof-of-concept (POC) study (see Annex B). A POC-Coordination Team monitored compliance with ethics approval processes during the study. This included a feasibility assessment to decide which databases fulfilled the study data requirements. The PE-tool was found to be practical for the study management to assure that all the required approvals were obtained.

The concrete recommendations concerning data protection and privacy are the following:

- The template guidance document for ethics approval and data sharing (Annex C) should include a protocol laying down the rules of engagement for all actors who access/contribute data, and a template for data protection and privacy impact assessments;
- In the event of a public health emergency study protocols should be submitted for ethical approval before fingerprinting is started;
- That these procedures are made permanently available on a central platform.

Training

It was clear from the ADVANCE project that there is a need for further training of experts engaged in benefit-risk analyses of vaccines using electronic health database, focused on legislation and codes of practice regarding i.e. privacy, ethics approval, data protection, code of conduct, etc.

Recommendations for future development

Future use of the platform would require training in those and similar areas for team members and other stakeholders regarding privacy, ethics approval, data protection, code of conduct.

Step 9. Extraction and transformation of data

This chapter describes the general steps in collecting and transforming data. The process is depicted on Fig. 5. Once the available and usable databases have been identified, the next step is to extract and transform their contents into a format that makes it possible to analyse the data in a merged fashion.

One of the most difficult challenges in creating an integrated harmonised framework for information generation is the diversity in the content and coding of medical conditions and procedures in the electronic health care data sources (applies to negative as well as positive clinical outcomes).

First, study-specific data are extracted into a simple common data model (CDM). The data in this CDM can be used in the fingerprinting step (the actual running of characteristics on the population, event and vaccines in the database using standardised scripts) and subsequently for studying coverage, safety, and benefit.

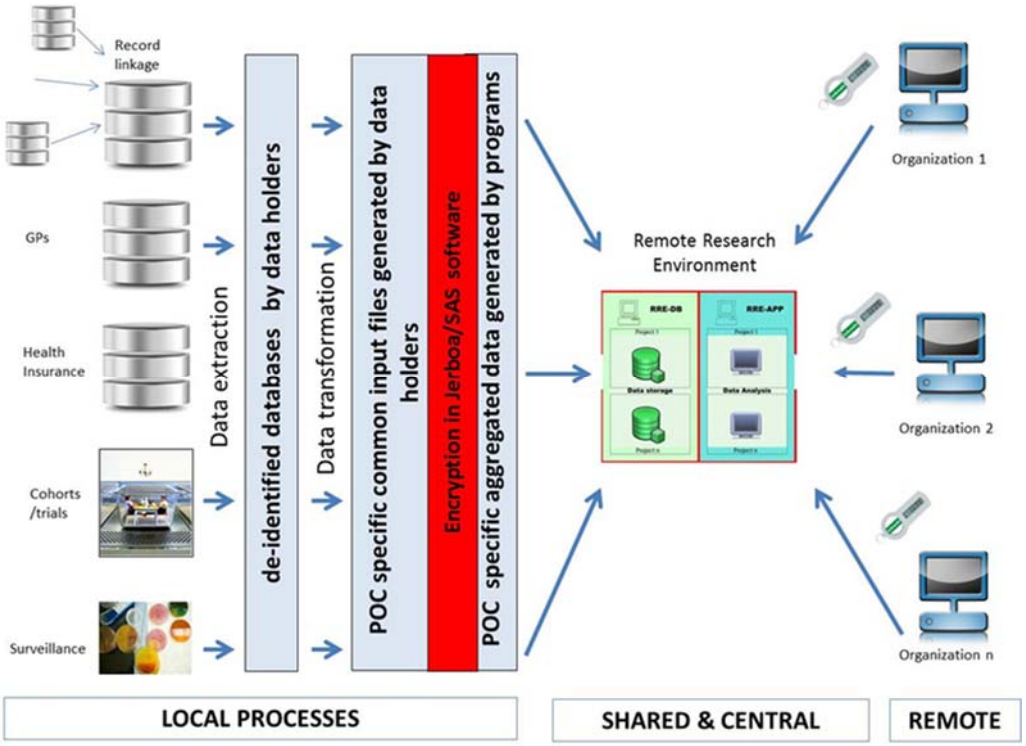

Figure 4. *Data collection and transformation*

Different coding schemes for medical events (e.g. International Classification of Diseases (ICD9-CM and ICD10), the International Classification of Primary Care (ICPC), and the Read Code (RCD) classification) and different sources of information (e.g., general practitioners' records, hospital discharge diagnoses, death registries, laboratory values, etc.) are available in various healthcare databases. For this reason, it is not easy to construct a single, completely reusable data extraction algorithm for the medical events in all the databases, or for that matter to transfer all content into a single common data model.

To reconcile differences across disease terminologies (plus free text), the ADVANCE project built a shared semantic foundation for the definition of events under study by selecting concepts from the Unified Medical Language System (UMLS) and mapping them to codes using a code mapping tool, for example the application CodeMapper[39] (see Becker et al, p. 26 above)

In the next step, one common standardised parameter-set is developed per study, using e.g. Jerboa[40] or software in SAS or R, tailored to the desired analysis, and this software is applied to the data that has been transformed in tables consistent with the common data model.

The software then encrypts, aggregates data, and generates study specific encrypted analysis tables that should be transferred and managed (e.g. by the "Octopus" infrastructure[41]) in a secure Remote Research Environment (RRE).

[39] https://euadr.erasmusmc.nl/CodeMapper

[40] https://www.ncbi.nlm.nih.gov/pubmed/21182150

[41] https://onlinelibrary.wiley.com/doi/full/10.1111/joim.12159

The RRE should be accessible remotely by all partners contributing data and those requesting access through a secure token and after signing for confidentiality. This would allow for shared and distributed analyses of studies. The model would allow for different data environments such as record linkage databases, electronic medical records, surveillance data, but also cohorts and trials or hospital based ad hoc data collections to transform content in a standardized manner. The model will be flexible regarding the type of underlying data and open to accommodate additional databases if and as they become available. Security and archiving of data on the RRE needs to be guaranteed.

The steps thus include:

- Developing standardised parameter nomenclature,
- Extracting data according to the common coding/nomenclature from chosen databases into a central repository that complies with required security and data protection standards,
- Ensuring the study teams have access to the repository, and
- Ensuring appropriate archiving and disposal arrangements.

Quality assurance and control principles in line with best practice guidelines and vaccine manufacturer standards need to be developed.

Step 10. Data analysis

A benefit/risk assessment should always start with a structured qualitative assessment to ensure that all elements of the benefit-risk balance have been considered and rendered explicit, thereby improving transparency and communication in decision-making.

The tools used for qualitative assessment are attribute trees followed by tabular summaries. The attribute tree is noteworthy given its ease of use and listing of the different benefits and risks. A generic example of an attribute tree for vaccines is shown below (Figure 4).

The tabular summaries then take as their starting columns the terminal branches of the attribute tree.

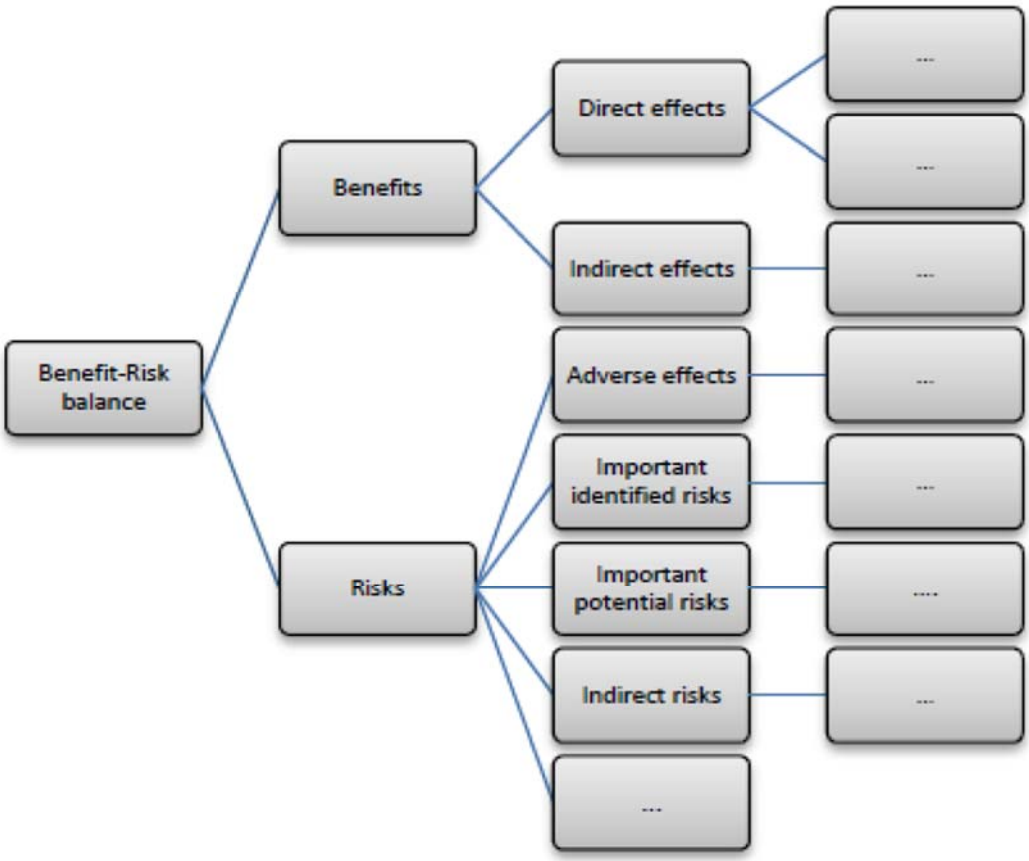

Figure 5. *Attribute tree for qualitative benefit-risk assessment of vaccines*

For quantitative estimates of benefit/risk, the ADVANCE project proposes the use of multi-criteria decision analysis (MCDA).

MCDA provides a highly structured approach which allows assessing and integrating multiple benefits and risks criteria and comparing multiple options. MCDA can be applied to benefit-risk assessment of vaccines given that special consideration is paid to the vaccine specificities, such as the time horizon, low risk tolerance, and the high levels of uncertainty. Multiple effects tables might be needed to summarise the evidence for vaccines with a substantial public health impact (e.g. one for vaccine uptake of 30%, one for an uptake of 50%).

A particularly valuable aspect of MCDA for vaccines is that it can accommodate many types of inputs or attributes. The ability to include continuous endpoints, dichotomous endpoints, categorical attributes and even more complex inputs could be potentially very important when combining information from heterogeneous sources, such as clinical trials, epidemiological studies, observational data analyses and infectious disease models.

A challenge for users of MCDA is that there are many MCDA methods available which makes the choice of MCDA method in any given context such as healthcare decisions quite complex. For a "complete" quantitative MCDA the treatment effects e.g. results from clinical trials, are combined with explicit weights for stakeholders' preferences between the treatment benefit and risk criteria. MCDA allows both benefits and risks to be split into multiple criteria. Overall weighted scores are calculated by multiplying the treatment effects by the weights and the result can be examined for uncertainty with sensitivity analyses.

MCDAs are often challenging to conduct because they require knowledge of various methods for modelling the clinical treatment value and eliciting stakeholder preferences to select the most appropriate for any given assessment. Weights are needed for each branch of the value tree.

There are other methods for B/R assessment available, some of which may be more tested and better recognised. One example is the use of 'Quality-adjusted life years' (QALYs) or 'Disability-adjusted life years' (DALYs) described above.

Both types of methods build on assigning a number to various types of quality or disability, which requires value judgements and is often problematic. Weighting can either be done by general public being asked to state how much quality of life would be decreased by a certain condition, or by experts.

Detailed description of methods of analysis of vaccine benefit, safety or coverage studies, is beyond the scope of this paper. They depend on the specific chosen study design variant and can be found in the subject literature.

Step 11. Developing a communication strategy

There are four steps in developing a communication strategy about the BR of vaccines for public-private collaborations. Optimally, a team of communication experts should adapt it into their existing communication strategies in response to newly emerging information about vaccine benefit-risk.

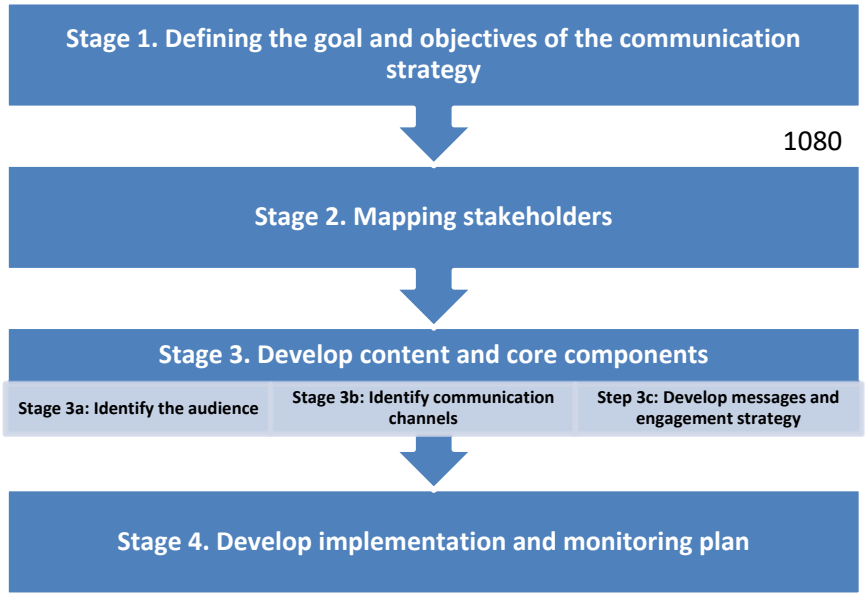

Figure 6. *Steps of developing a communication strategy*

11.1 Defining the goal and objectives of the communication strategy

Both the goal and objectives should be set according to SMART criteria: specific, measurable, appropriate, realistic and time-bound. The SMART criteria enable the communication team to

identify which audience they should target, what they intend to communicate and why particular information should reach that audience. The team in charge of communication strategy should design the goal/objectives. However, once the stakeholders are mapped (stage 2), all the involved stakeholders should collaboratively make improvements towards the definition of the goal/objectives.

There are special issues to consider when public and private organisations work together. The ADVANCE project provides guidance for organisations part of public-private collaborations (PPCs) on developing communication strategies on vaccine benefit-risk.

Objectives based on the goals can vary depending on the different groups of targeted audience. The deliverable D1.12[42] demonstrates different objectives for research organisations, manufactures, public health institutes, and regulatory authorities.

11.2 Mapping stakeholders involved in communication strategy development

At this stage, the stakeholders should be identified based on the particular area addressed by the benefit-risk monitoring/study. They usually include public health institutes, medicines regulators, academia, pharmaceutical industry, patients' and consumers' organisations, other groups from different research projects in the same area, scientific and non-scientific media, and general public including specified group's representation.

Stakeholders differ from "users" who will be using Blueprint to develop communication strategy, and also differ from the targeted audience.

All the involved stakeholders should contribute to developing the communication strategy collaboratively. Holding a workshop could be the method of engaging all involved stakeholders and a detailed list of stakeholders with their roles/responsibilities/interest should be created and updated throughout the workshop.

11.3 The public's perspective

The communication with the general public has to follow different steps:

- Listen. The system has to allow a place where the general public can ask questions and find appropriate answers.
- Educate. Through carefully chosen vocabulary, the general public can be educated and learn about scientific, medical and health issues. Vaccination is an important matter and there is a need of fluent communication between scientists that produce information and the public that receives it. Accurate information is mandatory as well as the need of highlighting the demonstrated benefits of vaccination. It is important that a team of experts are able to transform scientific data into accessible interpretation and easy terms for the general public.
- Inform. All of the communication channels have to be reached: media, apps, alerts on cell phones, videos, etc. There is a need of a constant update of the informative channels so that the general public is aware of the last news. There is also a demand from the patients of accurate and current data.

[42] http://www.advance-vaccines.eu/?page=publications&id=DELIVERABLES

- Adapt. The communication has to be fluent and dynamic in a pandemic situation or during an outbreak. The ADVANCE project has to be useful when an unexpected situation occurs.

Any communication activity also has to respect the public's interest in understanding how conflict of interests and bias are avoided in the benefit-risk monitoring, in particular given a context of a public-private collaboration (PPC).

11.4 Identifying the content of the communication

All the stakeholders at this stage will work on the concrete content of the communication, based on the project and its goal/objectives developed under stage 1. One important factor in designing the contents of the communication is whether the communication is intended to assist healthcare professionals, individuals, or policy makers making decisions based on vaccine benefit-risk.

A well-structured communication strategy should also be based on the understanding of communication environment. Three components should be identified to develop the strategy:

11.4.1 Identify the primary and secondary audiences

The audience is not a passive information recipient, it is considered as an active stakeholder in the communication strategy. The primary audience refers to people who are directly affected by the vaccine benefit-risk information, while the secondary audience includes those who receive information indirectly and those who can influence the primary audience. Both audiences should be precisely selected to initiate an effective communication.

11.4.2 Identify the communication channels

Based on the selection of audience, communication channels and tools should be identified aiming to reach audience and communicate with them effectively (Table 1).

Table 1. *Communication channels and corresponding tools*

Communication channels	Characteristics	Tools
Interpersonal channels	• One-to one contact Highly trusted by individuals Difficult to implement	Peer, family or provider counselling. Include using posters, brochures or facts sheets.
Community-based channels	• Wider group within a community • Participatory and engaging • Costly to scale up and needs adaption	Community participation activities and/or community media.
Mass media channels	• A large audience • Rapid, repeated, multi-channels and multi-languages.	Advertising, publicity, printed media, TV, radio and social media.

	• Trustworthiness can be questioned.	

11.4.3 Messaging and developing an engagement strategy

A key message should be tailored to the selected audiences and delivered by chosen channels/tools. It needs to be designed in such a way that it reaches and impacts the targeted audience effectively. It requires a clear, short, simple message holding the main idea, and thus needs to be designed by a special creative team which should also be counted as a stakeholder.

11.5 Developing an implementation and monitoring plan

Monitoring the implementation and evaluating its impact is a part of the communication strategy. The monitoring plan focusses on logistics and immediate impact; and the evaluation aims to assess the effectiveness of a communication intervention. Both are the decisive steps to identify if the communication strategy needs to be revised towards the goal/objectives. The monitoring and evaluation plan should define:

- Performance indicators
- Methods
- Responsible person and resources
- Timings
- A mechanism for notifying findings and recommendations to those responsible for follow-up action

The Deliverable D1.12 also provides two in-depth studies to illustrate the communication strategy, based on the ADVANCE proof of concept study 1.

3. Sustainability

The aim of the ADVANCE project has not been to actually build a specific structure for running B/R studies in the future, but rather point to possible solutions. An important issue for the Blueprint is thus the sustainability of the framework for rapid integrated post-authorisation benefit/risk assessment of vaccines.

In the elaboration of various possible sustainability models, the experience of EU Member States running immunisation programmes was built up through past /continuing ECDC initiatives including projects like I-MOVE, VENICE, SpIDnet, rotavirus vaccines impact study, and VAESCO. Moreover, the current ADVANCE project team includes a large group of stakeholders with a wide range of expertise and experience, specialised in establishing and running numerous health-related monitoring and surveillance programmes on a sustainable basis. Finally, results of some projects related to vaccines under IMI and Horizon 2020 would be important for the sustainability described in the Blueprint. Eventually there should be a sustainable financing mechanism at EU level to ensure that all the project-based activities described in this document can continue.

This section of the Blueprint defines its sustainability and key components; discusses options for post-ADVANCE sustainability models; and outlines performance indicators by which such models might be assessed. All the information provides background for the choice of the optimal mechanism.

3.1 - Definition of sustainability

In the context of EU projects, a sustainable project is one for which the perceived return on investment is considered to attract relevant stakeholders to maintain a commitment to support the project such that it has the resources required to continue to deliver benefits to the project beneficiaries and/or other constituencies for an extended period after the Commission's financial assistance has been terminated.

Several dimensions of sustainability may be identified, including financial (continued financial support or revenues), institutional (continued governance and managerial support), logistical (continued maintenance and human resources) and community (continued involvement of partners and stakeholders). All these dimensions are addressed in each sustainability model outlined below.

The fundamental question of "what needs to be sustained" must firstly be answered. In the case of ADVANCE, the framework would ensure the provision of a set of tools, data sources, and coordination mechanisms that researchers could use to generate risk/benefit and other analyses. It would specifically include an operational coordination system (central hub) and a suite of resources (tools and data sources) for researchers to use, with options according to the type of study and the organisation taking the lead. Depending on the problem to be addressed and the method chosen, different sets of inputs and outputs might be defined within the framework. The framework aims at enabling research rather than producing the risk/benefit analysis outputs. It does not include the actual research teams implementing the Blueprint or undertaking the studies and funding.

Substantial components of what need to be sustained are defined. For example, when it comes to governance, the ADVANCE project has already identified five key functions (Table 2). How and by whom these functions would be performed are key concerns when discussing institutional and logistical sustainability. On the other hand, the methodology developed by ADVANCE is still at the

proof-of-concept stage; further implementation may be needed before a fully refined model emerges. Likewise, there may already now be a need for evaluation of the framework, to check if it meets needs and standards. Such evaluations should be taken periodically.

Table 2. *Five key functions of governance*

Decision making	Assumes ultimate responsibility for the project, leading on its strategic direction, allocating funds and resources and making decisions for the project
Technical / scientific advisory	Provides recommendations for technical, scientific and related ethical aspects of the project
Implementation/ management	Implements and executes the project under the oversight of the decision-maker
Quality control	Controls, audits and advises on governance and quality of the project
Finance	Manages funds devoted to the project

3.2 - Approaches to sustainability post-ADVANCE

This section outlines four approaches to sustainability for further consideration.

- The "toolbox" approach: The creation and maintenance/update of an open-access toolbox for rapid integrated benefit/risk studies of vaccines). This model might include, for example, study design options and generic protocols, a code of conduct, governance models for studies, rules for interaction between study stakeholders and a directory of databases with key characteristics. The tools would be available in the public space and would be used on an open-access basis as needed, based on the principles set out in the Blueprint which users should comply with. According to this approach, financial and human resources would be provided by the stakeholders on a per-study basis, and the governance model would be selected depending on the types of participating stakeholders.
- The "project" approach: A further instance of time-limited funding by a funding organisation would be used to undertake a range of rapid integrated post-authorisation benefit/risk assessments of vaccines, according to the principles set out in this Blueprint. The aim here would be to leverage the results of ADVANCE, and provide valid and credible outputs from all ADVANCE stakeholders. Here, financial resources would come from a project budget and the governance model would be selected depending on the rules determined by the funding source, possibly from the range of ADVANCE governance models.
- The "network" approach. This approach would include a distributed network of stakeholders/researchers with access to databases. They could rapidly agree, in case of an urgent need for benefit-risk assessment of a vaccine, on common definitions of events, definition of research questions, coordination of protocol development and ad hoc study conduct, and rapid communication of results. Such a network would be based on a core group of the current participants of ADVANCE and would use the "toolbox" (as in option 1 above). Here, financial resources would have to be found on an ad hoc basis when there is an urgent need for "re-activation" of the network. The optimal governance model would be selected

from the range of ADVANCE governance models based on the types of participating stakeholders.

- The "central hub + platform" approach. A specifically mandated and suitably funded central hub would coordinate a network of stakeholders, and manage an EU electronic platform for running benefit/risk studies. The hub would use a system of data sources that allows joint analyses and would also manage a quality assurance system for data and results of analyses. The roles of various stakeholders in the network would be defined within the governance model(s) elaborated by WP1 of ADVANCE. A governance model would have to be acceptable to the stakeholders participating in the "hub+ platform" system. Sources of sustainable funding would have to be identified.

These approaches are not mutually exclusive. The "toolbox" (option 1) would be an integral part of any other approaches, which are assumed to use all or many options of the tools developed by the ADVANCE project.

Table 3 below provides a first assessment of the options outlined according to the main dimensions of sustainability identified above.

Table 3. *First assessment of the prospects for sustainability of the options outlined*

	Financial	Institutional	Logistics	Community
Toolbox	Least resource-intensive, though burden partly shifted to users. Funding or in-kind contributions still needed for maintenance/update.	Users in charge of decision-making. However, independent technical/scientific advice and quality control must still be assured (not least to reassure database owners that standards are adhered to).	Rapidly available for use. Users in charge of implementation. However, systematic arrangements for maintaining/updating databases, protocols, etc. still required.	Creation of lasting European partnerships would largely depend on ad hoc cooperation among users/stakeholders.
Project	Relies on a further instance of time-limited funding. The question of long-term sustainability will arise again at the end of the project.	Straightforward to continue with the current governance model and assure adherence to Blueprint standards.	Straightforward in principle to continue, although managerial and operational support from all partners may not be guaranteed.	The ADVANCE community in its present form is preserved for the time being.
Network	Limited need for base funding, but the burden would fall partly on participating	Definition of roles and decision-making on an ad hoc basis.	Flexible. However, no central administration means day-to-day management would	Preservation of at least a core group of ADVANCE participants and stakeholders.

	stakeholders/partners. Resources for quality assurance, expansion of data sources, training of investigators, etc. are still required.	Technical/scientific advice and quality control (and acceptance by data providers) would still need to be assured, though similarities with the current model may make this easier than under the pure toolbox model.	fall to stakeholders and partners.	
Central hub + platform	Requires sustained funding for central hub, though this may ease the burden on users/partners compared with other options.	Well-defined governance, roles, rules for interaction and procedures. Hub coordinates technical/scientific advice and quality control.	Availability of dedicated trained staff.	Perhaps the best prospect of preserving the ADVANCE community. However, need to identify committed partners to be involved on a continuous basis.

All approaches have their pros and cons. For instance, the toolbox approach (option 1) may seem less demanding financially, but the costs for users and database owners including the cost of assuring scientific and technical quality outside the present ADVANCE framework, should not be underestimated. The project approach (option 2) is appealing in some respects, but repeated project funding provides only temporary sustainability and each project approach will be competitive. Working through a network of stakeholders (option 3) has proved to be a sub-optimal approach in the past (e.g. at times of vaccine safety crises) owing to the length of time needed to make this operational and to deliver results if the platform, data and people capacity is not maintained. With the Blueprint in place, this option should deliver more rapid results, provided that partners and stakeholders are able to assume the necessary administrative and financial responsibilities.

The central hub+platform approach may seem to be the most demanding in terms of base resources, but may also be the most conducive to continuity of the ADVANCE framework in the long-term. The following section elaborates on the central hub + platform approach. If this option were deemed not to offer sufficient value, a permanent stakeholder network might be seen as a fall-back option.

3.3 - Central hub + platform approach

This is the preferred/optimal approach for sustainability. The overall objective of the central hub and platform approach is to put a validated framework for rapid provision of robust evidence on vaccine benefits and risks into practice, to support decision-making. The development of the framework will not cease with the Blueprint. The objectives of the hub should also include (among others) assistance to local databases, promotion of capacity-building, and further development of methods.

The mission of this approach is to provide a trusted platform (tools, methods, data and expertise) to support real world evidence on vaccine benefit/risk. It should sustain, expand and facilitate multi-stakeholder collaboration in Europe for post-licensing vaccine monitoring. This approach builds on the experiences and capacity acquired during the ADVANCE project:

(a) the coordinated network of centres used to work together

,(b) set of consolidated and well characterised data sources, used during the project

(c) set of validated methods for study of vaccine outcomes (coverage, effectiveness, safety, benefit-risk)

(d) familiarity with the ADVANCE code of conduct and governance practices developed as part of the project.

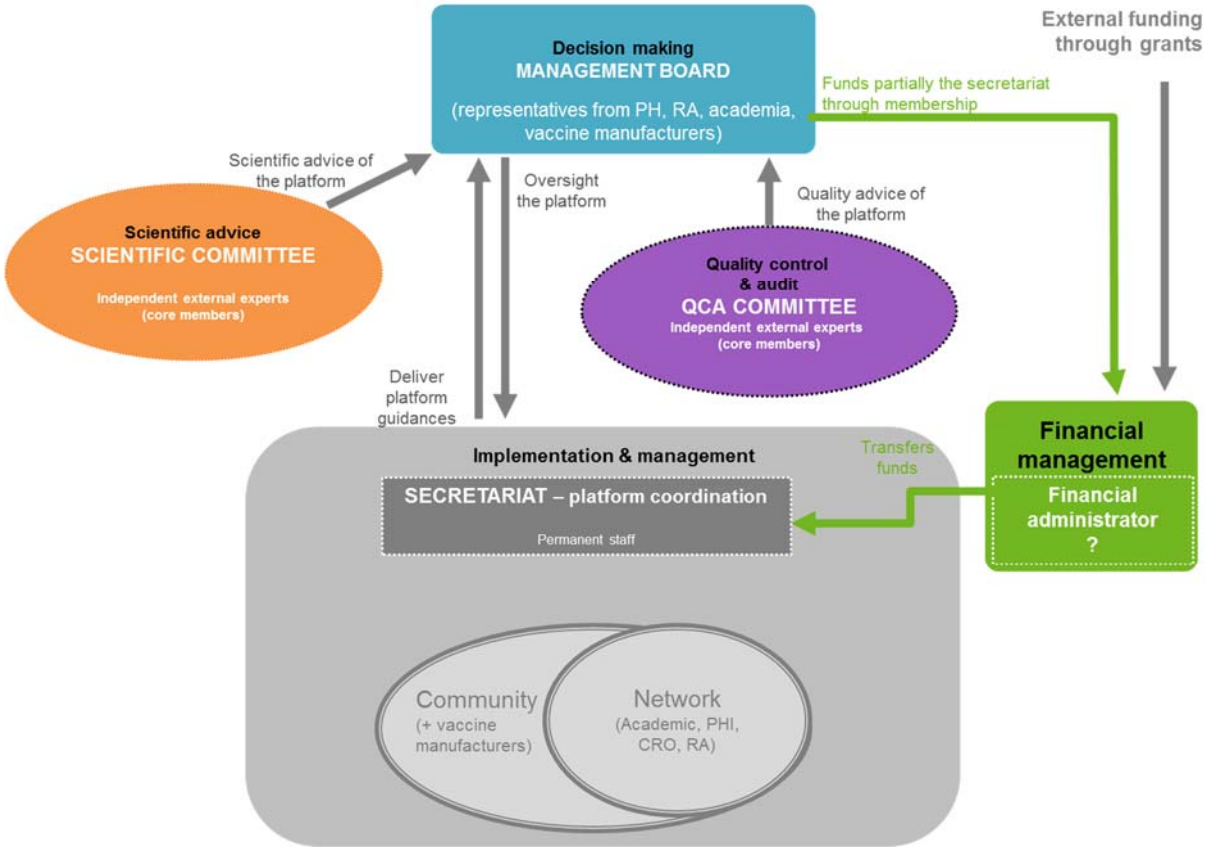

Figure 7. *Possible model for the "central hub +platform" approach.*

The *central hub +platform* model would consist of a scientific committee, a quality control and audit committee, management board, a secretariat, and a study network. If a specific study would need to be performed, a study operation centre will be activated along with two committees.

The management board would work with the secretariat through which strategic decisions will be operationalised. The board is proposed to consist of representatives of the main stakeholders interested in benefit-risk studies of vaccines and will include e.g. representation of public health, regulatory sector, academia, vaccine industry, patient associations and others. Specifically, its tasks will include:

- Strategic development (scientific and business)
- Conflict of interest management & governance oversight
- Evaluation of new organisations/centres who would want to join
- Framework/platform promotion
- Funding advice

It is important that organisations representing patients are also invited to be part of the management board. As a link to the public, they can also use the framework in helping to build trust in vaccines. Media often turn to these organisations and rely on them for providing perspective on vaccine issues. Including them can ensure that the communication regarding to vaccines is accurate, reliable and transparent.

A further task of the management board would be to review proposals for use of the platform. It is envisaged that potential future users would write a study synopsis that will be submitted to the management board for consideration and approval. Here, the management board would be assisted by the closely linked scientific committee.

Some criteria for selection of studies would be:

- Urgency
- Feasibility (e.g. sufficiently large study population)
- Cost
- Study plan
- Scientific experience of the study team
- Lack of previous studies

The central hub would be coordinated by a (semi-)permanent secretariat. The secretariat would be neutral of any stakeholder, but may tentatively be hosted (initially at least) by a project partner or stakeholder, and consisting of a small number of dedicated, trained staff. Its main external function is to serve as a contact point for potential study requesters. Internally, the hub will play a significant central role in communication and coordination with the study network, the community of stakeholders and the study operation centre. The activities and functions of this secretariat include:

Network coordination activities:

- Administration of the study network, day to day coordination
- Management & eligibility of expressions of interest for studies & matchmaking for joint/collaborative studies
- Coordination of requests for scientific studies
- Coordination of further development of capacity and methods by network members

Facilitation of management board/quality control and audit committee/scientific committee:

- Provision of governance advise, templates of contracts etc.
- Maintenance & coordination of revisions of ADVANCE code of conduct/governance/best practice

Site readiness

- Organisation of fingerprinting data sources
- Education of centres in methods, tools and workflow
- Maintenance & dissemination of ADVANCE IT tools/web applications

The study network refers to a network of data access providers and organisations who can undertake vaccine benefit and risk studies. The 'platform' in this context refers to the research platform comprising available databases and a network of researchers using those databases for future benefit-risk studies of vaccination ("Network" model described above). The network tasks would include:

- Methods and tool development
- Data converting and pooling (to take place in a GDPR-proof central environment)

Based on the need from requesters and interest/experience of certain organisations in the study network, a study operation centre would be formed and activated to operate the specific studies of vaccination. Thus, study requesters and the centre, together with the scientific and audit committees, would establish a study team to implement a specific study concerning vaccination (e.g. a full benefit-risk analysis). The functions of the study operation centre will include:

- Study outline
- Selection of partners from the network
- Feasibility assessment of data sources
- Protocol development
- Coordination of statistical analysis plan & programming
- Coordination of analysis & reporting
- Interactions with the requester(s)
- Contracting
- Budgetary management
- Study quality control and communication with scientific/audit committee

As regards platform governance, the central hub would fulfil part of the implementation and management function as outlined in the model of governance developed by ADVANCE WP1. It should be underlined, however, that the tasks of *the hub are clearly separated* from those of the teams that will carry out the actual benefit-risk assessment studies on behalf of the platform, where various governance models will be needed, depending on the composition of stakeholders involved in the studies. Also worth noting is that, while the hub would help to coordinate scientific advice and audit/quality control, *the staff of the hub would not be directly involved in these (independent) activities*. On the other hand, through its role in day-to-day coordination and monitoring, the hub would play a valuable role in ensuring compliance with defined governance procedures.

As regards finance, while precise estimates are difficult to obtain, the costs of maintaining a central hub would be in the order of 500,000 Euro or less per year assuming a maximum of three staff members, a small office space, around 10 trips per staff member to EU/EEA countries to liaise with network members and database staff, plus an annual meeting of around 30 persons hosted by the hub.

Options for funding the hub and platform will depend on the precise model chosen, but could include the following (not necessary mutually exclusive):

- Costs of the secretariat covered through an endowed foundation.
- Partners/members pay a fee for the secretariat (as well as committing a minimum of in-kind resources to maintain the readiness of data and staff to conduct studies).
- Partners/members are reimbursed for staff, project management and data costs through funded projects (i.e. paid-for services such as benefit-risk studies, monitoring, analysis of coverage and safety data, etc., which would be commissioned by or offered to stakeholders such as vaccine manufacturers, regulatory agencies, public health agencies, SMEs, academia, EU Commission and agencies).
- Overheads on funded projects serve to finance the hub and maintain basic readiness of the platform.

Ideally the secretariat should be funded by public money, and it should be hosted by an independent institution.

Annex A – Code of Conduct

Minimum requirements that should be uniformly applied are usually identifiable by the modal verb "must" below. Recommendations that should be considered for implementation are identifiable by the modal verb "should". In case of a public health crisis requiring rapid action, investigators may focus on the "must" clauses.

Scientific integrity

All researchers involved in the study team should be qualified and experienced scientists, acting in accordance with the values of science, including honesty, accuracy, efficiency, objectivity, transparency. The study team must perform its work objectively, without predetermined outcomes and using the most appropriate techniques. The recommendations of the ADVANCE Code of Conduct are intended to safeguard the scientific integrity of the studies and how they are perceived.

Transparency

1. Every vaccine benefit-risk study must be registered in a publicly accessible database before the start of study data collection or extraction. The EU PAS Register should be used for this purpose. Registration should include the study protocol or outline of the protocol providing enough information to understand and evaluate the methods used in the study.
2. Sources of research funding must be made public and specified in the study protocol and any presentation of results. All financial and non-financial public and private supports for the study should be documented.
3. Declaration of Interests (DoI) must be publicly disclosed at an early stage of the study. Potential interests must be declared in the study report and in publications.
4. In case of primary data collection, the subjects who participated in the study or their representatives are entitled to receive the main study results.
5. A final study report should be uploaded into the publicly accessible database where the study is registered (e.g. the EU PAS Register).
6. Other unpublished study information should be made available to researchers from outside the study team in an open and collaborative approach (for access to data, see section "Sharing of study data").
7. Recommendations from the external advisory board must be made available as soon as possible to all participants in the study, including the study requester and the study funder.

Conflicts of interest

1. Actual or potential conflicts of interest must be identified and addressed at the planning phase of the study in order to limit any possible undue influence on its design and support the credibility of the study team and results.
2. All Declarations of Interest (DoI) must be publicly disclosed at the time of joining the study team and must be updated at least once a year and immediately in cases of a significant change.

Study protocol

1. A protocol must be drafted as one of the first steps in any research project.
2. A detailed draft protocol should undergo independent scientific review by experts that did not participate to its writing and are not anticipated to be directly involved in the study as investigators.

3. The protocol must include a section with the ethical considerations involved and information regarding funding, institutional affiliations, potential conflicts of interest and data protection.
4. The protocol must include a description of the contribution of each party to the study design, the writing of the protocol and the study work programme with information on timelines, data source, data access, publications and authorship.
5. For studies on authorised medicinal products with involvement of the marketing authorisation holder, regulatory obligations and recommendations applicable to the study must be addressed in the protocol.
6. The protocol may be amended and updated as needed throughout the course of the study. Amendments or updates to the protocol after the study start must be documented in a traceable and auditable way.
7. The study protocol must follow an internationally-agreed format in order to ensure that all important aspects of the study design are covered and to facilitate its writing, assessment and review.
8. Statistical analyses should be described in an analysis plan to be finalised before data collection or extraction.

Study report

1. Responsibilities as regards the study report must be clearly established, including on the primary responsibility for writing interim and final reports and the possibility for persons from outside the study team to provide comments. This plan should be incorporated into the study protocol and research contracts.
2. A number of principles must be followed for reporting results:
    - Any deviations from the analysis plan must be clearly documented in the report; additional analyses which are deemed necessary based on initial ones must be presented as such.
    - Outcomes resulting from changes to the analysis plan after data analysis has begun must not be used for the purpose of verifying or rejecting the prior hypotheses of causal association stated in the protocol but may be used to generate further hypotheses.
    - Interpretation of statistical measures, including confidence intervals, should acknowledge potential sources of errors and limitations of the study. Sensitivity analyses should be conducted.
    - Investigators should present how missing and non-interpretable data were handled.
3. Interpretation of the research results of an analysis of secondary data is the responsibility of the user of secondary data. The data custodian may be invited to provide comments.
4. The intermediate results of the study may be presented or published only subject to a procedure approved in advance. Intermediate results must always be explicitly presented as such.
5. The STROBE statement should be considered when analysing and reporting data.
6. It is recommended to present the study report in an internationally-agreed format. Sources of funding, affiliations and any potential conflicts of interest must be declared in the final report.

Publications and scientific communications

1. Attempts should be made to publish as soon as possible results in a peer-reviewed scientific journal Presentations at meetings are not substitutes for publications in the peer reviewed literature.
2. The publication policy must be agreed in advance and included in the protocol and the research contract. The principal investigator must be able to independently prepare publications based

on the study results irrespective of the funding or data source. The requester, funder and data custodian should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. These comments should be documented.

3. Procedures must be put in place to rapidly inform competent authorities of the results of the study, irrespective of the submission of a manuscript for publication.
4. All relevant study results must be made publicly available, irrespective of the results. Information published must be accurate and complete. In no circumstances should the results be changed. Unless there is an urgent public health issue, the results of a study should undergo independent peer review before they are made public or the media are informed.
5. In cases where the study is discontinued for any reason, the presentation or publication of any preliminary or partial results or conclusions may be presented or published but the results from a discontinued study must be identified as such.
6. Authorship of publications must follow the rules of scientific publication published by the International Committee of Medical Journal Editors (ICMJE).

Subject privacy

1. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information. In a study with primary data collection where personal/identifiable data are needed, the study protocol must include a justification for the need for such data and a document that informed consent from the study subjects has been obtained and that agreement from the relevant ethical committee has been granted.
2. In case where personal data are collected or used in a study, provisions of the relevant legislation, in particular of Regulation (EC) No 45/2001 and Directive 95/46/EC, must be followed.

Sharing of study data

1. An open and collaborative approach to study data sharing with the scientific community from outside the study team should be followed. Data sharing will normally concern only the anonymised analytical dataset. Data should normally be shared only after the study report is finalised.
2. Sharing of study data should be based on a written request specifying the ground of the request, the nature of the data requested and a protocol on the analyses to be conducted. The written request should normally be preceded by informal discussions on the reasons for the request and it acceptability and feasibility. It is the responsibility of the study team to verify the compliance of the request with the data protection legislation and to seek approval or ask advice from concerned persons or committees, including, if relevant, the steering committee, the data controller, the data custodian and the ethics committee.
3. Requests to data sharing must be made on specific grounds with a justification based on the interest for public health. The decision to share study data lies at the appropriate level of the study governance (study team or steering committee). The public health objective of the request and the scientific quality of the protocol must be important elements to be considered.
4. Analyses performed with shared data must follow the ADVANCE Code of Conduct, including the Declaration of Interests (DoI) by the data requester.
5. Sharing of study data may be subject to a contractual agreement specifying that the data will not be used for other purposes than those defined in the protocol and referring to the ADVANCE

Code of Conduct. The data requester may be asked for fair compensation for dataset preparation or analysis of data.

Research contract

1. A research contract must never lead investigators or other entities, directly or indirectly, to violate the principles of the Helsinki Declaration for medical research, or act against applicable legal or regulatory obligations.
2. A research contract must specify that the study will be conducted according to the ADVANCE Code of Conduct.
3. Key elements of any research contract are clarity and transparency: all relevant aspects must be covered in a way that is understandable and acceptable by all the parties concerned.
4. Research contracts must indicate that the study will follow the recommendations of the ADVANCE Code of Conduct.

In the Code of Conduct, attempt has been made to differentiate between requirements that have to be followed to ensure validity and credibility of the study results and recommendations that should be considered for implementation. A consensus on the use of “must” and “should” for different aspects of the Code of Conduct will be an important next step for the development of the ADVANCE Code of Conduct. For this reason, it is intended to perform a broad public consultation.

Annex B - Privacy and ethics assessment for specific vaccine studies

Objectives: Collect data on the process of ethical approval, data protection and privacy to support investigators looking to conduct vaccine effectiveness or safety studies to help steer them through the ethical handling of data throughout data collection, linkage and integration

Study Title:

This questionnaire relates specifically to the protocols in the first proof of concept studies of ADVANCE project (please tick all the studies in which your organization will participate in some form)

- Testing new approaches to monitoring benefit/risk with pertussis vaccines as test case. Coverage rates of acellular and whole-cell pertussis-containing vaccines in preschool children (Coverage study)

- Testing new approaches to monitoring benefit/risk with pertussis vaccines as test case: Incidence rates of benefit outcomes of whole-cell pertussis and acellular pertussis vaccines in pre-school children (Benefit study)

- Testing new approaches to monitoring benefit/risk with pertussis vaccines as test case, Incidence rates of safety outcomes of whole-cell pertussis and acellular pertussis vaccines in pre-school children (Risk study)

- POC study protocol: The benefit-risk of pertussis vaccines in children comparing whole cell and acellular formulations (Benefit/Risk analysis)

Type of organization

1) How do you categorize your organization?

- ☐ Research organisations (including academic and other)
  - o Profit
  - o Non-for profit
- ☐ Public Health Institute
- ☐ Regulator Agency
- ☐ Vaccine manufacturer
- ☐ Contract research organization
- ☐ Foundation/charity
- ☐ other

2) What is the responsibility for your organization in these POC studies (please select more than one if applicable)

Coverage study

- ☐ None
- ☐ Principal investigator
- ☐ Statistician/programmers
- ☐ Study team member in other role
- ☐ Data custodian/ controller
- ☐ Funder
- ☐ End user
- ☐ Other…….

Benefit study

- ☐ None
- ☐ Principal investigator
- ☐ Statistician/programmers
- ☐ Study team member in other role
- ☐ Data custodian/ controller
- ☐ Funder
- ☐ End user
- ☐ Other…….

Risk study

- ☐ None
- ☐ Principal investigator
- ☐ Statistician/programmers
- ☐ Study team member in other role
- ☐ Data custodian/ controller
- ☐ Funder
- ☐ End user
- ☐ Other…….

B/R analysis

- ☐ None
- ☐ Principal investigator
- ☐ Statistician/programmers
- ☐ Study team member in other role
- ☐ Data custodian/ controller
- ☐ Funder
- ☐ End user
- ☐ Other…….

3) What type of the study are these POC-I studies from the perspective of your organization

- ☐ Observational

☐ Interventional

If Interventional is the study:

☐ Randomised ☐ Non-randomised

For organizations contributing data (data custodian)

4) What type of data collection will be used from your site for this study/studies

☐ Primary data collection for this study
☐ Secondary use of data collected for other purposes than this study
☐ Other…….

5) What type of data does your organization hold that can be used for the POC-I studies

☐ Population data (national or regional or patients covered)
☐ Inpatient diagnoses from hospitalization registry
☐ Primary care medical record
☐ Outpatient diagnoses from specialist care
☐ Laboratory data (claims)
☐ Laboratory data (measurement & results)
☐ Prescribed drugs outpatient
☐ Prescribed drugs inpatient
☐ Dispensed drugs
☐ Childhood vaccinations
☐ Influenza vaccinations
☐ Travel vaccinations
☐ Other…….

6) Can clinical conditions (such as pertussis or safety outcomes) be validated by accessing medical records/charts

☐ Yes (go to 6-a)

☐ No

☐ Do not know

6a) In order to validate clinical conditions, how can access to medical records be obtained for you as co-investigator?

☐ Administrative procedure (third party), no patient consent required

☐ Through treating physician, no patient consent required

☐ Through patient consent

☐ Patient having the option to opt-out

☐ Other…….

7) Would data linkage of your population and medical outcomes database with an external registry (not residing in your organization) be needed to provide optimal data for the POC studies? (e.g. to vaccination registries?)

☐ Yes, and this is possible
☐ Yes, and this is not currently possible (please provide reason)……
☐ No, not needed all the required data are available in the databases we hold (Go to 9)
☐ Other…….

8) Is additional approval (if any) required for data linkage?

☐ Yes
☐ No

8a) What is the timeline and process for this approval process?

Please describe……

8b) How would linkage be conducted

☐ Deterministic (Patient or national identification number)

☐ Probabilistic: combination of multiple variables (birthdate, gender, Postcode, etc.) that are in common

8c) Who would conduct the linkage

☐ Your organization

☐ the other organization

☐ A trusted third party (please give name……..

☐ Other……

8d) Are any additional data protection measures in place for the processing of linked data?

Please describe……

8e) What additional time commitment is necessary to implement these extra measures (weeks per process)?

Please describe……

8f) Do you need to do an official privacy impact assessment for the linkage or any other formal documentation?

Please describe……

Storage, sharing and archiving

9) What is the level of privacy in which you store your data in the research version of the database you hold?

- ☐ Pseudo-anonymised / coded (you can go back to patient if needed)
  - ☐ Key is held by your organization
  - ☐ Key held by external organization (e.g. third party)
- ☐ Anonymised (no possibility to go back to patient anymore)
- ☐ Identifiable (unique personal identifiers, name and address details or any other sensible data available to researchers)

10) Data can be shared with other organization with the following conditions

- ☐ Individual level (e.g. one record per patient)
  - ☐ If coded (de-identified)
  - ☐ If anonymised (not possible to go back to the patient in the organization that will received the data)
- ☐ Aggregated results with a certain minimum of cases in one cell
- ☐ Aggregated results (no threshold)
- ☐ Do not know

11) If the level of privacy of data sharing is satisfactory, where can you send data?

- ☐ Across institutions - Nationally
- ☐ Across countries

If across countries, is the data sharing allowed

☐ Within the EU ☐ Outside of EU

12) Does the ability to share data differ according to the background of the principal investigator? (public sector, private industry researcher, academic researcher?) Please indicate how this process may differ.

_____
_____
_____
_____

13) Can you archive the databases from which study data will be extracted for at least five year?

☐ Yes

☐ No

☐ Do not know

14) Do you have a written standard operating procedure for archiving data?

☐ Yes

☐ No

☐ Do not know

15) Approval processes of protocol

15) To which committee did you need to submit the protocols

None (please go to 15 a)

Ethics committee (please give name)……..

Data governance board (please give the name)……..

Scientific review committee (name)……

Data protection agency……

Other ……

15a) If you are a data provider

Can you provide a written statement that you can participate to the studies without separate review?

16) How long did the approval of the protocols take from submission to approval, for each approving body?

For Ethics committee, _____(weeks)

For Data governance board (please specify), _____(weeks)

For scientific review committee, _____(weeks)

For data protection agency, _____(weeks)

For other …… (weeks)

17) Can you please provide a copy of all approvals received for study archiving?

☐ Yes

☐ No

18) Do you have comments about issues that arose in the approval processes, that can be a learning for the next POC?

……