Innovative Medicines Initiative

www.advance-vaccines.eu

Accelerated Development of VAccine beNefit-risk Collaboration in Europe

Grant Agreement nº115557

D1.13 White paper[1] (recommendations) from WP1 for the final blueprint: governance guidance and Code of Conduct

WP1 – Best practice and code of conduct for benefit- risk monitoring vaccines

V1.0 Final
29 September 2017

Lead beneficiary: WP1
Date: 29/09/2017
Nature: White Paper
Dissemination level: PU

[1] *Disclaimer: the opinions summarised in this report are those of the authors and do not necessarily reflect the opinion of the organisations they represent.*

Table of contents

Document information

Grant Agreement Number	115557	**Acronym**	ADVANCE
Full title	Accelerated Development of VAccine beNefit-risk Collaboration in Europe		
Project URL	http://www.advance-vaccines.eu		
IMI Project officer	Angela Wittelsberger (angela.wittelsberger@imi.europa.eu)		

Deliverable	**Number**	1.13	**Title**	White paper (recommendations) of WP1 for the final blueprint: governance guidance and code of conduct
Work package	**Number**	1	**Title**	Best practice and code of conduct for benefit-risk monitoring vaccines

Delivery date	**Contractual**		**Actual**	
Status	Current version / V1.0		Draft☐ Final x	
Nature	Report ☐ Prototype ☐ Other x			
Dissemination Level	Public x Confidential ☐			

Authors (Partner)	Laurence Torcel-Pagnon (SP), Xavier Kurz (EMA), Vincent Bauchau (GSK), Cédric Mahé (SP), Myint Tin Tin Htar (Pfizer), Anne Charrat (SP), Patrick Mahy (WIV-ISP), Marianne van der Sande (RIVM), Tyra Grove Krause (SSI) and François Simondon (IRD) Margaret Haugh for medical writing (MediCom Consult)			
Responsible Author	Laurence Torcel-Pagnon		**Email**	Laurence.pagnon@sanofi.com
	Partner	SP	**Phone**	+33 (0)607 450 398

Description of the deliverable	Recommendations paper from the work package on good practice guidance and governance models.
Key words	Governance, public-private collaboration, multi-stakeholders, vaccines, benefit-risk monitoring

Document history

NAME	DATE	VERSION	DESCRIPTION
Laurence Torcel-Pagnon	15 June 2017	Outline	First draft
Myint Tin Tin Htar, Laurence Torcel-Pagnon, Xavier Kurz, Vincent Bauchau, Marianne van der Sande, Patrick Mahy, Tyra Grove Krause, Margaret Haugh	16 June 2017	Outline	Meeting in Paris to discuss main comments received and agree on final governance proposals and white paper content/structure
Laurence Torcel-Pagnon	19 June 2017	Outline	Update
Myint Tin Tin Htar, Xavier Kurz, Vincent Bauchau, Marianne van der Sande, Patrick Mahy, Tyra Grove Krause, François Simondon, Anne Charrat, Cédric Mahé, Margaret Haugh	20 June 2017	Outline	Comments
Laurence Torcel-Pagnon	20 June 2017	Outline	Final
ADVANCE Coordination team	29 June 2017	Outline	Approval
Laurence Torcel-Pagnon, Margaret Haugh	11-25 July 2017	V0.1	Development
Laurence Torcel-Pagnon, Margaret Haugh, Xavier Kurz, Vincent Bauchau	27 July 2017	V0.1	TC
Margaret Haugh	7 August 2017	V0.2	Integration of comments
Xavier Kurz, Vincent Bauchau	8 August 2017	V0.2	Comments
Margaret Haugh	21 August 2017	V0.3	Integration of comments
Laurence Torcel-Pagnon, Xavier Kurz, Vincent Bauchau	23 August 2017	V0.3	Comments and TC
Margaret Haugh, Laurence Torcel-Pagnon	28 August 2017	V0.4	Integration of comments
Laurence Torcel-Pagnon, Xavier Kurz, Vincent Bauchau	29 August 2017	V0.5	Comments
Margaret Haugh, Laurence Torcel-Pagnon	30 August 2017	V0.6	Integration of comments
Myint Tin Tin Htar, Xavier Kurz, Marianne van der Sande, Tyra Grove Krause, François Simondon, Anne Charrat, Cédric Mahé, Vincent Bauchau,	11 September 2017	V0.6	Comments
Margaret Haugh, Laurence Torcel-Pagnon	11 September 2017	V0.7	Integration of comments
Miriam Sturkenboom, Patrick Mahy, Xavier Kurz	22 September 2017	V0.7	SC review and comments

NAME	DATE	VERSION	DESCRIPTION
Laurence Torcel-Pagnon , Myint Tin Tin Htar, Xavier Kurz, Marianne van der Sande, Tyra Grove Krause, Anne Charrat, Vincent Bauchau	22 September 2017	V0.7	TC to discuss integration of comments
Laurence Torcel-Pagnon, Margaret Haugh	26 September 2017	V0.8	Integration of comments
Myint Tin Tin Htar, Xavier Kurz, Vincent Bauchau, Marianne van der Sande, Patrick Mahy, Tyra Grove Krause, François Simondon, Anne Charrat, Cédric Mahé,	28 September 2017	V0.8	Final comments and validation
Laurence Torcel-Pagnon, Margaret Haugh	28-29 September 2017	V0.9	Integration of final comments
Myint Tin Tin Htar, Xavier Kurz, Vincent Bauchau, Marianne van der Sande, Patrick Mahy, Tyra Grove Krause, François Simondon, Anne Charrat, Cédric Mahé,	29 September	V1.0	Final version approved

ADVANCE consortium[2]

- Participants in the ADVANCE Consortium are referred to by the following abbreviations:

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spain)
ASLCR	Azienda Sanitaria Locale della Provincia di Cremona (Italy)
ARS Toscana	Agenzia Regionale di Sanità, Toscana (Italy)
AUH	Aarhus Universitetshospital (Denmark)
CRX	Crucell Holland BV (Netherlands)
ECDC	European Centre for Disease Prevention and Control (Sweden)
EMA	European Medicines Agency (United Kingdom)
EMC	Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
GSK	GlaxoSmithKline Biologicals, S.A. (Belgium)
IDIAP JORDI	Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut
GOL	Jordi Gol i Gurina (Spain)
IRD	Research Institute for Development (France)
JANSSEN	Janssen Vaccines & Prevention B.V. (Netherlands)
KI	Karolinska Institutet (Sweden)
LSHTM	London School of Hygiene and Tropical Medicine (United Kingdom)
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
OU	The Open University (United Kingdom)
NOVARTIS	Novartis Pharma AG (Switzerland)
P95	P95 (Belgium)
PEDIANET	Società Servizi Telematici SRL (Italy)
PFIZER	Pfizer Limited (United Kingdom)
RCGP	Royal College of General Practitioners (United Kingdom)
RIVM	Rijksinstituut voor Volksgezondheid en Milieu* National Institute for Public Health and the Environment (Netherlands)
SEQUIRIS	Sequiris (The Netherlands)
SP	Sanofi Pasteur (France)
SP MSD	Sanofi Pasteur MSD (France)
SSI	Statens Serum Institut (Denmark)
SURREY	The University of Surrey (United Kingdom)
SYNAPSE	Synapse Research Management Partners, S.L. (Spain)
TAKEDA	Takeda Pharmaceuticals International GmbH (Switzerland)
UNIBAS	Universitaet Basel (Switzerland)
UTA	Tampereen Yliopisto (Finland)
WIV-ISP	Institut Scientifique de Santé Publique (Belgium)

[2] The ADVANCE Consortium, comprising the legal entities listed here (draft 2)

Abbreviations

ADVANCE	Accelerated Development of VAccine beNefit-risk Collaboration in Europe
B/R	Benefit Risk
CoI	Conflict of Interest
CRO	Contract Research Organisation
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
IMI	Innovative Medicines Initiative
MAH	Marketing Authorisation Holder
NITAG	National Immunisation Technical Advisory Group
PHI	Public Health Institute
PPC	Public Private Collaboration
RA	Regulatory Authority
WHO	World Health Organisation

Definition of Terms

The definition of terms used in governance can vary depending on the area of interest, such as public facilities, environment or defence. We have decided to use simple terms and definitions throughout this report. Definitions related to scientific independence, scientific integrity, transparency and conflict of interest can be found in the ADVANCE Code of Conduct and are used accordingly in this document.[3]

Governance: a set of processes for interaction and decision-making among the partners involved in a project.

Partner: an organisation that contributes resources, funds, facilities, expertise, data, workforce or any other contribution to a project, signs the project contract and can expect to obtain benefits from the project results.

Project: one or several studies or other long-term activities designed to address vaccine benefit-risk monitoring in post marketing settings.

[3] Kurz X, Bauchau V, Mahy P, Glismann S, van der Aa LM, Simondon F. The ADVANCE Code of Conduct for collaborative vaccine studies. Vaccine. 2017;35:1844-55.

Public-private collaboration (PPC): an engagement of public and private organisations, who share common interests in vaccine B/R monitoring, to work together in a project. The roles and responsibilities of each partner organisation are agreed and formalised through a contract agreement. This could be a short-term (study specific) or a long-term broader project. The responsibility for the project can be attributed to either one stakeholder, who will be the decision maker, or shared between two or more partners, through a steering committee with partner representatives and defined voting rights. *Note: We have decided to use the term PPC rather than 'public-private partnership (PPP)' because in the PPPs that we know, decision-making is always shared between partners, whereas in ADVANCE's PPC guidance model, the decision-making function can be either under the responsibility of one partner or shared between partners. As such PPC is a broader term which includes PPP.*

Stakeholder: an organisation (e.g., regulatory authority, public health institute, research institution, contract research organisation, vaccine marketing authorisation holder, data access provider, patient association and civil society organisation) who has interests in the benefits and risks of vaccines and vaccination programmes.

Study: detailed investigation carried-out to answer a well-defined research question on vaccine benefit-risk monitoring in post marketing settings.

Study team: a group of individuals, not organisations, who are responsible for the scientific and operational decision-making concerning the implementation of a specific study. Each study team member should have adequate education, training, experience and expertise to fulfil their specific role in the study implementation. The study team will contribute collectively to the design, feasibility assessment, execution, interpretation and reporting of the study, and ensure compliance with the principles of scientific integrity and transparency throughout the study life-cycle.

Trustee: an organisation that holds and administers property or assets for the benefit of a third party. The trustee is a legal entity without any financial interest in the results of the project that has the competence and right to channel funds in a transparent manner between the funder(s) and partner organisations. The trustee is not the funder.

1. Executive summary

The pandemic influenza crisis in 2009-10 and the new European pharmacovigilance legislation have changed how vaccine post-marketing monitoring should be done in Europe and have demonstrated the need for collaboration, in particular, between public and private organisations, to sustain or improve some aspects of the post-marketing surveillance and, ultimately, to maintain confidence in immunisation.

The aim of ADVANCE, an Innovative Medicines Initiative (IMI) project, is to establish a framework that could rapidly provide robust post-marketing data on vaccine benefit-risk (B/R) to support decision making in Europe. The ADVANCE consortium, composed of public and private stakeholders from national public health institutes (PHI), European Centre for Disease and Control (ECDC), European Medicines Agency (EMA), national health regulatory authorities, research institutes, contract research organisations (CROs), small and medium enterprises (SMEs) and vaccine marketing authorisation holders (MAHs), is a unique forum for key stakeholders in vaccines to establish common rules for future public-private collaborations.

The objective of this white paper is to present two components of our best practice guidance to support vaccine benefit-risk monitoring in Europe: a Code of Conduct for collaborative vaccine studies and a governance guidance for transparent, ethical and trustable public-private collaborations (PPCs) and provide recommendations based on lessons learnt during the ADVANCE project. The ADVANCE Code of Conduct and governance guidance have different objectives. The Code of Conduct is a set of good practice principles that should be adopted by individuals working in organisations collaborating to perform vaccine studies. The governance guidance describes how collaborative projects could be structured and how organisations could interact (including the decision-making process) to facilitate the execution of the project and collaboration between partners. They both fulfil the key principles of strengthening public health, scientific integrity and transparency.

This white paper is intended for those wishing to develop collaborations between public and private stakeholders for vaccine B/R monitoring in Europe. It aims to provide, in a common language, the necessary level of information and understanding needed for implementing governance for PPC projects. The generic, flexible governance model with options enabling stakeholders with a shared objective to design their own governance, based on the context and specificities of their project developed by ADVANCE, is described. The guidance includes recommendations of how stakeholders' concerns, such as scientific independence and public trust, can be addressed.

2. Introduction

2.1 The need for good practice guidance and collaboration in vaccine benefit-risk monitoring

Vaccination is acknowledged to be one of the most effective and widely used public health interventions, providing demonstrated individual and community benefits. Since vaccines are complex biological products generally administered to healthy individuals they have specific safety and effectiveness considerations. A new vaccine has to demonstrate its quality, efficacy and safety to obtain a marketing authorisation. However, at this time there will be limited data concerning vaccine effectiveness and adverse reactions in real life settings. Robust systems and procedures must therefore be in place to continuously monitor the quality, safety and effectiveness of vaccines after their authorisation and marketing. At the EU level, post-authorisation evaluation of the benefit- risk profile of vaccines is an ongoing process under the responsibility of vaccine MAHs and national health regulatory authorities. As part of their mandate, public health authorities also continuously evaluate the benefits and risks of their vaccination programmes.

Thus vaccine benefit-risk monitoring projects 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.

These projects may have to face 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 containing the results for disease confirmation and/or the strain of the infectious agent), some of which have strictly restricted access.
- The need to implement robust systems and procedures that 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 or rare disease events and take into account demographic and geographic factors when estimating the benefits and risks of vaccines, which may require data collection from several countries.

During and following the 2009 pandemic influenza, key stakeholders in the field of vaccines such as national health regulatory authorities, national public health institutes and vaccine MAHs faced multiple challenges, limiting their individual capacity to rapidly collect and assess European data on vaccine exposure, safety and effectiveness to make informed decisions on the benefit-risk. Issues included lack of rapid access to available data, difficulties to establish efficient interactions between multiple stakeholders, lack of confidence between

public and private stakeholders, concerns about perceived and real conflicts of interest, heterogeneous communication and lack of funding mechanisms for multi-stakeholder studies.

Timely vaccine benefit-risk monitoring projects 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.

Box 1: Some examples of real-life objectives that may require public private collaborations

Objective: To validate a safety signal (e.g. from spontaneous reporting) urgently • Confirmation can require information from different countries and partners to increase size • Available data collected by PHIs or research institutes (e.g., vaccination coverage, background incidence of safety event) and by MAHs (e.g., vaccines doses distributed, vaccine content, safety database) • Infrastructures to manage, analyse and pool data
Objective: To monitor safety/effectiveness after the introduction of a new vaccine • Requires large data sets from geographically-wide settings • Need to understand heterogeneity in different countries • Both PHIs and MAHs have responsibilities in the post-marketing settings • Need for specific knowledge from clinical trials from vaccine MAHs, and from disease surveillance from PHIs
Objective: To improve rapid communication in the event of a crisis or unexpected changes in vaccine B/R: • PPC will provide a network for discussion and development of common message and aligned communication that will be more believable by the general public

2.2 Objective of this white paper

The objective of this white paper is to present two components of best practice guidance to support vaccine benefit-risk monitoring in Europe: a Code of Conduct for collaborative vaccine studies and a governance guidance for transparent, ethical and trustable public-private collaborations (PPCs) and provide recommendations based on lessons learnt during the ADVANCE project.

2.3 The ADVANCE project

ADVANCE[4] is a 5-year project that started in October 2013 with 47 public and private partners working together under the IMI framework to develop and test a framework that could provide robust post-marketing vaccine benefit-risk data to support decision-making in Europe. The ADVANCE consortium, composed of public and private stakeholders from national public health institutes (PHI), European Centre for Disease and Control (ECDC), European Medicines Agency (EMA), national health regulatory authorities (RAs), research institutes, contract research organisations (CROs), small and medium enterprises (SMEs) and vaccine marketing authorisation holders (MAHs), is a unique forum for key stakeholders in vaccines to establish common rules for future public-private collaborations.

2.4 Guidance development process

Guidelines for the governance of public-private collaborations exist in some areas, such as defence and the basic sciences or for the management of big and complex structures such as the Global Fund, IMI or GAVI. However, at the study or project level in the public health sector, only informal governance structures, established on a case-by-case basis, exist.

An ADVANCE Code of Conduct working group was established to develop a code of conduct that provides recommendations for studies involving several public and private partners willing to work in collaboration. The development of the code of conduct was guided by a review of existing guidance and relevant publications and three core and common values (best science, strengthening public health and transparency). Recommendations relevant for the code of conduct were extracted from the guidance identified in the review and additional recommendations were developed by the working group, as needed. The resulting draft was made available for public consultation via the ADVANCE website and the 386 comments received from 20 non-ADVANCE organisations were taken into consideration in the final Code of Conduct.

In parallel, an ADVANCE Governance working group was established to work jointly on guidance for the governance for public-private collaborative projects on B/R monitoring of vaccines. The working group was composed of representatives from key stakeholders (co-authors of this white paper and named in the Document history section above). As a starting point, existing governance models and guiding documents were evaluated to identify governance structures applicable to the context of vaccine B/R monitoring[5]. The definitions, functions and bodies in the governance structure were adapted to fit with ADVANCE scope.

Scenarios frequently encountered by the co-authors (taking into account different real life research questions and contexts) were used to discuss and describe the added value and challenges of PPCs and to clarify functions, roles and responsibilities of the different stakeholders and prerequisites for governance bodies (Box 2). Draft governance guidance was

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

[5] GAVI, Global Fund, IMI, McKinsey and Company – Public-private partnership Dec 2009

developed and a group of independent experts, mandated by IMI and a review panel, mandated by the ECDC, reviewed it and provided comments for future implementation.

Box 2: Two examples of scenarios used by the guidance working group for discussions

Scenario 1: A national regulatory authority requests a vaccine MAH to investigate the benefit-risk profile of its vaccine
Scenario 2: A national public health institute wants to conduct a study to evaluate the effectiveness of a vaccine within a vaccination programme

The working group acknowledged that public-private collaboration for vaccine B/R monitoring is challenging with a wide range of positions, particularly from the different national public health institutes in Europe. They recommended that ADVANCE should seek input from a broader group of stakeholders (additional national public health institutes, patient associations and additional countries) before finalising the guidance. The ADVANCE Governance working group organised a 2-day workshop in March 2017 at the EMA offices in London which was attended by almost 70 senior experts from various stakeholders.[6] The input from the workshop participants was reviewed and discussed within the full consortium. The ADVANCE Governance working group took the input into account to make adjustments and produced the final guidance presented in this white paper.

3. Code of Conduct

The ADVANCE Code of Conduct is a set of good practice principles that should be adopted by individuals working in organisations that are collaborating to perform vaccine studies.[7] For its development, 31 of the 44 guidelines and documents identified contained pertinent information on at least one topic in the ADVANCE Code of Conduct. Widely used codes of conduct include that from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[8], which provides standards for scientific independence and transparency of research. One of its provisions is that persons with a financial, commercial or personal interest in a particular study outcome should not take part

[6] Workshop report available at: http://www.advance-vaccines.eu
[7] Kurz X, Bauchau V, Mahy P, Glismann S, van der Aa LM, Simondon F. The ADVANCE Code of Conduct for collaborative vaccine studies. Vaccine. 2017;35:1844-55.
[8] http://www.encepp.eu/code_of_conduct/index.shtml

in any study activities once the protocol has been finalised, and therefore it does not provide guidance for the conduct of collaborative studies involving multiple partners, whoever they are, during the whole research process. Hence we considered that it was not comprehensive enough to meet the objectives of ADVANCE but its core principles of scientific independence and transparency were integrated into the ADVANCE code of conduct. Other important codes of conduct, i.e., the Good Pharmacoepidemiology Practices (GPP) from the International Society for Pharmacoepidemiology (ISPE) and the Good Epidemiology Practice (GEP) from the International Epidemiological Association (IEA)[9] do not address all the topics covered by the ADVANCE code of conduct but they were used as an important source for its development.

The ADVANCE Code of Conduct includes 45 recommendations for 10 topics: scientific integrity; scientific independence; transparency; conflicts of interest; study protocol; study report; publication; subject privacy; sharing of study data; research contract (see column 1 in Appendix 2). A definition, a set of recommendations and references for additional reading were provided for each topic. The concept of the study team was introduced as a key component of the ADVANCE Code of Conduct with a core set of roles and responsibilities. It is hoped that the adoption of the ADVANCE Code of Conduct by all partners involved in a collaborative vaccine study will facilitate and accelerate the study's initiation, design, conduct and reporting. Its adoption should be declared in the study protocol, study report and publications. In addition, journal editors are encouraged to use it as an indication that good practice principles of public health, science and transparency were followed throughout the study.[7]

Code of Conduct and governance guidance

Although they have different objectives, the Code of Conduct and the governance guidance fulfil the key principles of strengthening best science, public health and transparency. The table in Appendix 2 summarises how both documents include the 10 core topics of the Code of Conduct.

4. Potential benefits and risks for collaboration

There are numerous stakeholders in the post-marketing vaccine B/R monitoring environment in Europe, including ECDC, EMA, national PHIs, national RAs, public and private research institutes, data access providers and CROs. The public-private collaborations covered by this governance guidance are those involving the stakeholders who usually perform post-marketing vaccine B/R monitoring, which mainly means collaborations between all of these stakeholders.

[9] https://www.pharmacoepi.org/resources/guidelines_08027.cfm; http://ieaweb.org/good-epidemiological-practice-gep/

4.1 Potential benefits of public-private collaboration

Public-private collaboration should provide benefit for all partners in the collaboration, which should go beyond simply providing funds, data, facilities or expertise (see Definition of Terms). The collaboration considered here is not just one partner providing funding and another providing results, but rather partners who want to work together to share their collective expertise and resources for the project goals. Thus the collaboration should be built on the complementary and synergetic roles of the public and private partners while leveraging their assets.

It is essential to acknowledge the contribution and expertise from each partner organisation and the resulting synergy, while being transparent about potential conflicts of interest (Figure 1; Appendix 1). These collaborations could result in better use of existing resources which could also lead to potential financial savings. The collaboration between organisations should be built on mutual support and facilitate the sharing of knowledge, good practice and information.

Many stakeholders, including national PHIs, national RAs and vaccine MAHs share an interest to monitor the benefit-risk profile of vaccines and vaccination programmes. PHIs are responsible for evaluating the benefits and risks of their vaccination programmes and RAs are responsible for monitoring the quality, safety and efficacy of vaccines marketed in their territory. Because routine vaccine benefit-risk evaluation has become part of vaccine MAHs' regulatory requirements, they need such data not only to fulfil their regulatory obligations, but also to facilitate the development of safer and more effective vaccines.

Timely and robust post-marketing monitoring of vaccines benefits and risks is costly. As seen during the pandemic, public funding was not sufficient for the maintenance of such a system. Research institutes often have little structural funding and obtain funding from both competitive public funding and private funding to initiate projects.

Having access to the necessary data from large European population databases with information on vaccination can allow all stakeholders to study, observe and generate more robust results on the safety and effectiveness of vaccines and vaccination programmes. These databases, which include electronic repositories of routine data, sentinel networks or laboratory data, are owned by different stakeholders, such as ministries of health, public health institutes, research institutes, are usually accessible only through public health or research institutes. In parallel, vaccine MAHs have pharmacovigilance and clinical development databases with relevant safety information accessible only to regulatory authorities.

Because of each stakeholder's multiple interests, the main added value in a true PPC comes from the synergy arising from sharing expertise.

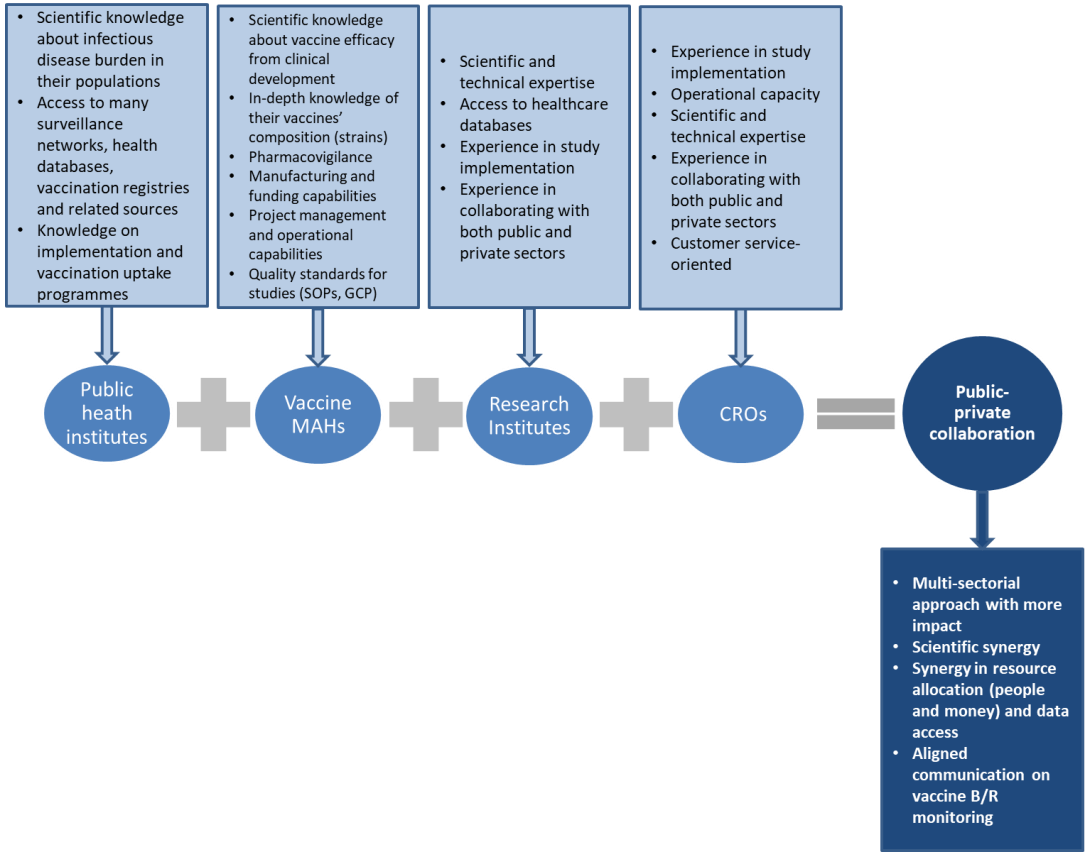


Figure 1: Potential synergy from public-private collaborations for vaccine benefit-risk monitoring

Bringing together professional and personal skills of individuals from various organisations with different scientific expertise and experience is an added value for collaborative research projects. In the context of vaccine benefit-risk monitoring, expertise and experience in research on vaccines, vaccination programmes, related infectious diseases and project design, conduct and analysis should be strengthened by the collaboration. The collaboration should facilitate scientific exchange and discussion which will lead to better quality studies that will provide more robust scientific evidence. It should also result in synergy for non-scientific aspects, such as rapidity and adherence to international standards and improved quality.

4.2 Potential risks of public-private collaboration

There is a need to evaluate the risks associated with public-private collaborations for public health advancement. The potential risks of public-private collaborations can be either common to all or specific to individual stakeholders.

The common risks include the fact that the interactions may involve a complex structure to comply with the internal procedures of the various stakeholders so that the benefits of collaboration may not justify the time and resources that have to be invested or the loss of flexibility in working practices. Depending on the governance structure selected, the stakeholders may feel a loss of autonomy and be frustrated with the complexity in the decision-making and potential conflict resolution processes. The different perspectives of the stakeholders, that are not always convergent, may require time to converge for the project goals. This could lead stakeholders to feel they are diverting energy and resources away from their core missions. Also, an unsuccessful project due to inability to resolve conflicts could be damaging for the stakeholders' organisations and be viewed as a waste of resources. A successful and trusted collaboration is one in which the participants are aware of the legal and regulatory obligations and constraints of each partner organisation and are willing to take the time to build and maintain trust between partners.

The specific risks for PHIs include their concerns about the perception of their scientific integrity and independence if they are seen to collaborate with vaccine MAHs which could lead to loss of public trust and potentially have an impact on their national vaccination programmes or even beyond. The study design for vaccine B/R monitoring studies, which is observation, does not minimise bias as well as that for randomised clinical trials; this could have an impact on the perception and trust of results. The risks associated with potential, real or perceived conflicts of interest need to be acknowledged and carefully considered. A plan to manage these risks is a prerequisite before initiating collaboration between PHIs and vaccine MAHs.

For vaccine MAHs, a specific concern, particularly in public-private interactions, is that the high level of regulations imposed on them for all their scientific activities may require time for alignment between all partners and effort to ensure compliance, traceability and documentation. In addition, if vaccine MAHs do not participate in the PPC their essential knowledge about the vaccine would not be used and their relevant databases not shared.

A risk for academic researchers is the loss of their perceived scientific credibility and independence. Their participation in a PPC may make them ineligible to act as independent experts for international (e.g., WHO, EMA, ECDC) and national bodies (e.g. national immunisation technical advisory groups (NITAGs) or national RAs), even if any financial gains would be received by their research institutes.

5. Governance guiding principles

In addition to the general principles described in the ADVANCE Code of Conduct,[10] the following guiding principles should be implemented for the project governance.

5.1 Efficiency

Formal multi-stakeholder initiatives are labour and time intensive, so the most appropriate form of collaboration should be carefully considered for each project and the public health and other gains, including organisation-specific gains, should be commensurate with the investment. All partners should have a clear understanding of why their objectives cannot be achieved as efficiently using other mechanisms. The governance model should be as simple as possible, transparent, acceptable to all partners, and appropriately-sized to ensure efficiency. It should be designed to achieve the objectives of the project efficiently, which may involve discussion and agreement on rules prior to setting up the PPC. The roles and responsibilities and decision making rules should be agreed between the partner organisations and included in the project contract.

5.2 Equity

The common and specific interests of the partner organisations, the project objectives and the vision of the initiative should be clearly stated and agreed. The structure and processes of the governance model should reflect mutual respect and shared benefits. The partner organisations' perspectives should be considered in the project objectives and the governance structure should ensure that their perspectives can be heard. The decision making process should reflect a fair balance of these perspectives.

5.3 Transparency

Participating organisations should ensure that individuals with relevant position, knowledge, motivation, skills and resources, including time available for the project, are involved in the project. This will be enhanced if participating organisations develop and

[10] Kurz X, Bauchau V, Mahy P, Glismann S, van der Aa LM, Simondon F. The ADVANCE Code of Conduct for collaborative vaccine studies. Vaccine. 2017;35:1844-55.

promote the scientific autonomy of their employees and reflect this in their internal governance policies and processes. Policies related to compliance with good practices, prevention of conflict of interest and scientific autonomy should be shared between partners and specific training to promote compliance with these should be provided.

All decisions, key communications and minutes from the various committees meetings should be documented to facilitate audit and monitoring of compliance. At project initiation, a communication plan should be developed and agreed between partners and pre-define escalation processes planned, in case of issues.

6. Fundamental governance functions

This section is here to ensure that our target audience, i.e. stakeholders wishing to develop European collaborations between public and private stakeholders for vaccine post-marketing B/R monitoring, have the necessary level of information and understanding of a common language needed for implementing public-private collaborations.

The proposed governance structure is articulated around five core functions which can be attributed to individual partner organisations or to a governance body or committee, with representatives from partner organisations (Figure 2). The roles and responsibilities of the individual partner organisations will be defined by the functions they assume in the structure.

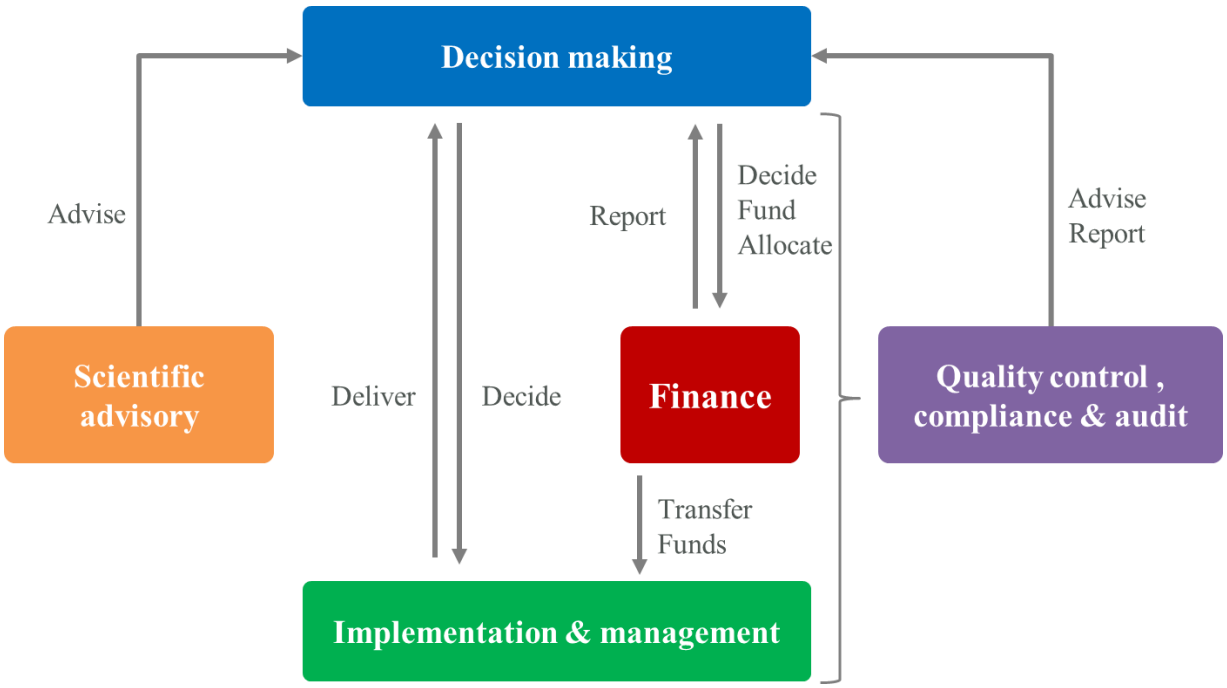


Figure 2: Simplified schematic representation of fundamental governance functions and their interactions

6.1 Decision making function

The decision making function will involve taking full responsibility for the project, and taking the lead on its strategic direction, allocation of funds and resources and making decisions related to the project. This function will include:

- responsibility for scientific, ethical, legal and compliance aspects of the project;
- overall project governance: endorsement of the work plan, high-level follow-up of progress in critical areas of the project and taking appropriate corrective actions, when necessary, and perform project contingency plans and risk management;
- allocating and reallocating budget and resources to keep the project aligned with its objectives;
- seeking advice from other parties or committees for technical, scientific, quality and compliance considerations;
- approval of project deliverables;
- management of external communication and advocacy related to the project and ensuring that project results are published and disseminated

6.2 Scientific advisory function

The scientific advisory function will involve making recommendations for the technical, scientific and related ethical aspects of the project to the decision making body. This function will include:

- providing advice and recommendations on technical and scientific topics to the decision maker.
- contributing to, reviewing and providing advice on scientific deliverables, e.g., research plan, protocol(s), analyses, interpretation of results, report(s), scientific communication and publications;

6.3 Quality control and audit function

The quality control and audit function will involve responsibility for the quality control and audit of the study and providing advice on the governance and quality of the project to the decision making body. This function will include:

- auditing the governance to ensure that the principles and rules of governance are respected:
    - verifying transparency of funding sources and funding allocation;
    - verifying transparency of the decision making process and appropriate documentation;
    - verifying adequate declaration of potential conflicts of interest; evaluating potential conflicts of interest; reporting any specific issues to the decision maker;
- ensuring adequate quality control and corresponding auditing:
    - verifying compliance with relevant guidelines, and national and international standards and requirements;
- overseeing project compliance
- reporting findings to the decision maker and provide advice, recommendations and proposed action plan, when needed.

6.4 Implementation and management function

The PPC project can involve one or more studies (see Definition of Terms). This implementation and management function (and associated operational decision-making) is at the study level.

The implementation and management function will be responsible for the implementation and execution of the study under the supervision of the decision maker. This function will include:

- managing daily operational aspects of the study, i.e., performing technical, legal (e.g., contract development) and administrative (e.g., ethics and data protection-related submissions) tasks under the decision maker's authority and liaison with the project partner organisations, as required;

- ensuring oversight of studies (either directly or through sub-contracting);
- producing scientific deliverables, e.g., research plan, protocol(s), statistical analysis plan(s), report(s), publications and other scientific communication

If the PPC project is simple, with a single study, the implementation and management function could be merged with the decision making function under the responsibility of one or more partner organisations and defined as the study team.

6.5 Finance function

The finance function will involve taking responsibility for the management of the project funds under the supervision of the decision maker. This function will involve:

- managing the budget with appropriate accounting and invoicing to ensure financial transparency and independency;
- distributing funds independently of funders, under the supervision of the decision maker;
- reporting on traceability of the funding sources and beneficiaries to the decision maker.

7. ADVANCE recommendations

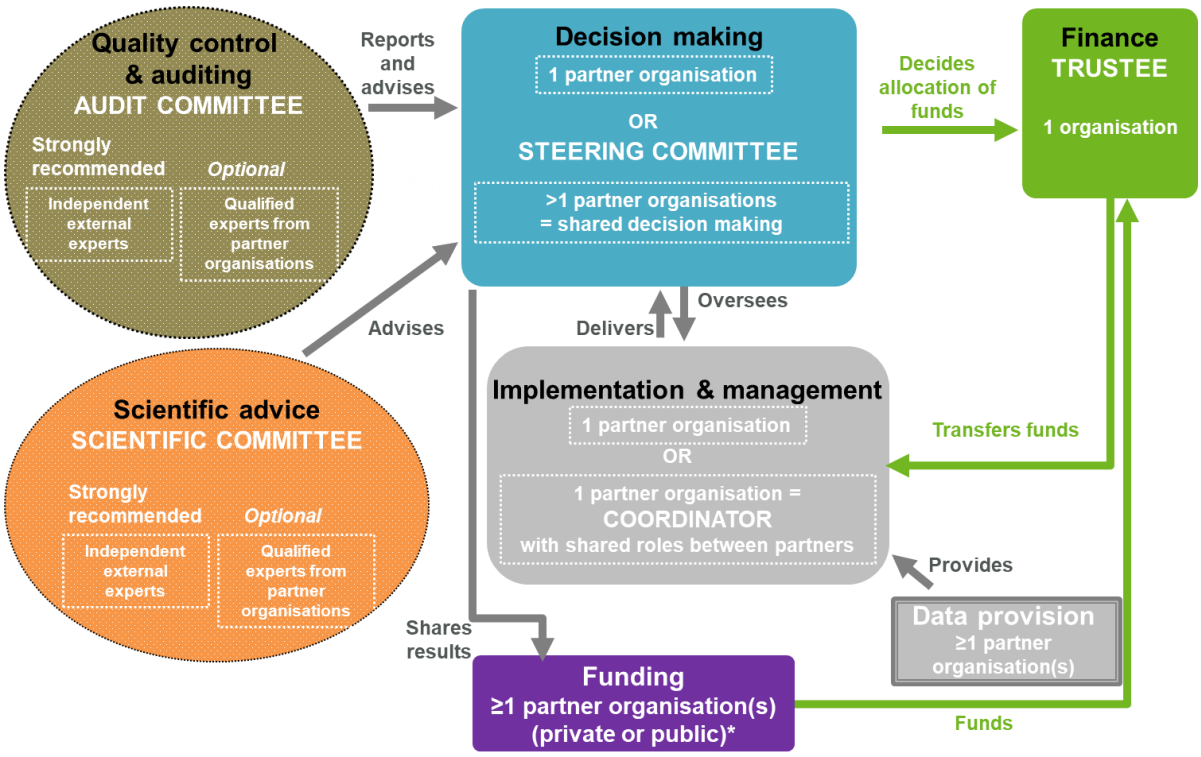
To achieve the potential added value and benefits from PPCs, and manage the potential common and individual risks presented in Section 4, ADVANCE has made several recommendations to support the implementation of transparent, ethical and trustable vaccine B/R monitoring projects in Europe.

7.1 Generic governance model

ADVANCE has developed a generic governance model with options to enable it to be used in as many situations as possible (Figure 3). It is clear that no single model exists and the generic model proposes a structure that can be adjusted to the needs of the scientific question and the project setting.

The generic model has the five core functions described in the basic governance model (Figure 2). While each governance body can be adapted to suit the specific situation for which the PPC is implemented, ADVANCE has produced recommendations about what type of partner can assume which role and their responsibilities.

The audit and scientific committees are pivotal for guaranteeing the project's scientific relevance, acceptability, ethics and transparency. Therefore these committees should be independent from the decision making and implementation & management bodies.



As a prerequisite of a 'veritable' PPC, the funder(s) should be partner organisations, which means that their involvement should go beyond providing funding. However, **additional project funding could be received from non-partner organisations; e.g. external funding through grants from research foundations, European commission.*

Figure 3: ADVANCE generic governance model for public-private collaborations for vaccine benefit-risk assessment projects

7.1.1 Decision making body

The decision making function can be attributed to a single partner (the decision maker) or to two or more partners as a shared decision making body (i.e., steering committee). If one partner takes on this role, this could be a national PHI, a national RA, a research institute, or the ECDC.[11] If a steering committee with shared decision making is included in the governance model, all partners can be included, and ADVANCE recommends, where possible, that the committee should reflect a balanced representation from the different public and private

[11] It would be possible to have a governance model in which the single decision maker is a vaccine MAH, but this would then be a project sponsored by the vaccine MAH and not a PPC.

partners and include representatives from patient associations and civil society organisations (as observers or with voting rights).

7.1.2 Scientific advisory body

As described in Figure 3, we strongly recommend that the scientific advisory committee is composed of independent external experts (experts from non-partner organisations) who act on their own and do not represent their institution or organisation. In some circumstances, duly justified by the need for specific expertise for the project, the decision maker may select qualified scientists from partners' organisations (PHIs, vaccine MAHs, research institutes, CROs). The role of these experts would be to inform on technical aspects of the project (e.g., vaccine characteristics, study design), but they should never represent the majority of the scientific advisory committee members. If the experts are employed by a partner organisation, they should not be involved in implementation or decision-making functions in the project.

The selection of scientific advisory committee members is the sole responsibility of the decision maker, using a transparent and documented process. Their roles and responsibilities should be clearly defined and agreed and their interests should be declared transparently.

The selection of each independent external experts should be duly justified and should be based on their relevant expertise on the specific question(s) (e.g., disease, vaccine) or their expertise in broader fields (e.g., drugs, outside Europe). They should be selected from organisations or institutions that are not partners in the collaboration, such as, other PHIs, research institutions, RAs, vaccine MAHs, ECDC, EMA, WHO, civil society organisations, and CROs. The selection of scientists from partner's organisations (PHIs, Vaccine MAHs, research institutes, CROs) should be based on their individual expertise relevant for the project question(s). For vaccine MAHs, the scientists should be independent of marketing and commercial operations departments.

This committee should not have any voting rights. They should provide scientific advice and make written recommendations (with traceability of the proposer(s)) to the decision maker. If the decision maker decides not to follow them, their reasons should also be clearly documented.

7.1.3 Quality control and audit body

As described in Figure 3, we strongly recommend that the quality control and audit committee is composed of independent external experts (experts from non-partner organisations) who act on their own and do not represent their organisation. In some circumstances, duly justified by the need for specific expertise for the project, the decision maker may select qualified persons from partner organisations (PHIs, vaccine MAHs, research institutes, CROs). The role of these experts would be to inform on quality and compliance aspects of the project, but they should never represent the majority of the quality control and

audit committee members. If they are employed by a partner organisation, they should not be involved in implementation or decision-making functions in the project.

The selection of members of the quality control and audit committee is the sole responsibility of the decision maker, using a transparent, documented process. Their roles and responsibilities should be clearly defined and agreed and their interests should be declared transparently.

The selection of each independent external expert should be duly justified and should be based on their specific expertise in compliance, public-private governance and quality processes. They should be selected from public and private organisations or institutions that are not partners in the collaboration such as, other PHIs, research institutions, RAs, vaccine MAHs, ECDC, EMA, WHO, civil society organisations, and CROs. The selection of experts from partner organisations (PHIs, RAs, vaccine MAHs, research institutes, CROs) should be based on their individual expertise. For vaccine MAHs, the experts should be independent of marketing and commercial operations departments.

This committee should not have any voting rights. They should provide quality control and audit reports, compliance advice and make written recommendations (with traceability of the proposer(s)) to the decision maker. Their findings and recommendations should be clearly recorded. If the decision maker decides not to follow their recommendations, the reason(s) for this should be documented.

It is recommended to set up the quality control and audit committee at an early stage to enable them to assess, manage and mitigate conflicts of interest and provide advice for the selection of the members of the scientific advisory committee.

7.1.4 Implementation and management body

The implementation and management functions could be attributed to one partner and the study team, as defined in the ADVANCE Code of Conduct[12], will comprise their employees. In this case, the partner could be a PHI, research institute, or a CRO with sufficient in-house expertise and time to assume these functions, under the oversight of the decision maker or steering committee. If the project is simple, with one study, these functions could be combined with the functions of the decision making body under the responsibility of one or more partner organisations.

Alternatively, one partner could coordinate these functions, and the study team can include employees with relevant expertise and dedicated time to work on the study team from other partner organisations. In this case, the coordinating partner could be any of the partners in the PPC with experience in running the specific type of study.

[12] Kurz X, Bauchau V, Mahy P, Glismann S, van der Aa LM, Simondon F. The ADVANCE Code of Conduct for collaborative vaccine studies. Vaccine. 2017;35:1844-55

7.1.5 Finance body

It is recommended to have a trustee to manage the financial assets, when PHIs and vaccine MAHs are involved in the PPC or when there are more than one funder or more than one country involved. The decision to have a trustee and the selection of the organisation to be a trustee should be discussed between the partners but the decision should remain under the responsibility of the decision maker. In all cases, the funder(s) should have no role in the allocation of funds to prevent undue influence on the implementation of the project. If the funder(s) are represented on the decision-making body, they should not have voting rights for funding decisions.
The function of the Trustee may vary depending upon the PPC model. It could be the partner organisation in charge of the implementation and management function or an independent organisation.

7.2 Role of patient associations and civil society organisations supporting vaccination

Promoting the active participation of patient associations and civil society organisations supporting vaccination in PPCs is highly recommended to support and enhance transparency and public trust in the context of vaccine B/R monitoring in a real-life setting and vaccination programme assessments. They may be an important bridge between the scientific experts and the lay public and their active participation may inform, reassure and contribute to improving public confidence in vaccines and prevent poor perception of conflicts of interest.

Depending of the project context and question(s), they could be involved in the PPC the capacity of:

- members of the steering committee either as observers or with voting rights;
- members of the scientific committee,
- members of audit committee, if they have appropriate qualifications and experience;
- independent external experts consulting for the review of project information dedicated to external communication to lay public.

7.3 Decision making rules

At the start of the PPC, the partners need to agree what decision-making process will be used at the project level to ensure delivery of the objectives.

Consensus is the preferred method of decision-making because it will generate better solutions and commitment from all. Seeking consensus will encourage the partners to find an agreement that incorporates all points of view. The appropriate timing for voting should also be agreed. Our recommendation is to have a consensus process, but to allow a majority voting process to enable a decision to be made, if consensus cannot be found. If a majority voting process is necessary, discordant viewpoints should be recorded with the final decision or deliverable.

We recommend that the quorum should be defined as two-thirds of members present and that the qualified majority vote should be set at 75% of the voters. It is strongly recommended to have an escalation process for when decisions cannot be reached or when major issues, concerns or objections are raised. This escalation process could involve seeking advice internally from the project advisory bodies (scientific committee or audit & quality control committee) or externally from other experts and non-partner organisations.

7.4 Risk management plan for conflicts of interest

The WHO has stated they are often faced with a combination of converging and conflicting interests when developing partnerships with non-State actors.[13] All actors generally have CoIs, which can be converging and conflicting and can be financial or non-financial. It is important to acknowledge this fact and evaluate the impact of the potential CoIs of all individuals and organisations on the project strategy, particularly the governance function(s) potentially affected. This means that an organisation or expert with potential or real CoIs could be excluded for functions that can be impacted by their CoIs, but they may assume other functions within the PPC that are not impacted.

We recommend that there is a continuous risk management plan for CoIs in the design of the governance model, under the responsibility of the quality control and audit committee. Declarations should be made at both institutional and personal levels, they should be updated during the project as circumstances change and they should be publically available. It is important to manage real and potential CoIs and, equally importantly, the perception of these. We recommend the use of risk management plans for CoIs that have been developed by other organisations, such as WHO, EMA, OECD.[14]

We recommend that the process should include the following steps:

- set up the quality control and audit committee as early as possible
- have a documented process for the declaration of CoIs and periodic updates at the individual and organisational levels
- evaluate the impact of the CoI on the project as a whole and on dedicated governance functions
- develop a risk mitigation plan

---

13 http://www.who.int/nutrition/topics/advisory_group/callforexperts_nugag_policyactions2017_guideline_declarationofinterests.pdf;

14 http://www.who.int/nutrition/topics/advisory_group/callforexperts_nugag_policyactions2017_guideline_declarationofinterests.pdf; http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000178.jsp&mid=WC0b01ac0580029338; http://www.oecd.org/gov/ethics/49107986.pdf.

7.5 Legal considerations for PPCs

By definition, a PPC should lead to mutually satisfactory outcomes. Each partner must provide a tangible contribution to the project. They must have legal rights granted to them, depending on the project and their level of the contribution. The basic principle of an efficient collaboration is, from the onset of the reflection, to agree to the sharing with all partner(s) of specific assets, data, knowledge or expertise and to agree to grant the relevant rights legal. The negotiation of the contract terms should be done freely and in good faith between all partners.

The ownership of results from the PPC and the rights to use them should be discussed on a case-by-case basis. Various solutions could be envisaged including co-ownership of results and various types of license for use. In all cases this should be agreed between stakeholders and clearly defined in the project contract before the project is initiated.

The plans for the dissemination and publication of the results from the PPC should be discussed to take into consideration the needs of each partner, before the project starts and should be described in the contract. In all cases, publications should comply with international guidance, such as the recommendations from the International Committee of Medical Journal Editors (ICMJE) and Good Publication Practices (GPP3).[15]

The right to privacy is a highly developed area of law in Europe (freedom of information acts, data protection laws and the European General Data Protection Regulation (GDPR[16])), which should be taken into consideration in all PPCs. Personal data should not be processed, except when certain conditions are met. Personal data are protected and the potential user or entity that has access to any personal data are controlled and audited to ensure compliance with the protection regulations. Consequently, the transfer of personal data is strictly regulated and partners cannot request more than what is allowed by law. The sharing of data is a sensitive aspect of the PPC and, therefore, the rules, clearly stating what can and what cannot be done in terms of data sharing should be included in the project contract.

To implement a sustainable and transparent collaboration, we recommend that the payment of any project funds should be made to a legal entity (an institution, organisation) and not to an individual to avoid potential fraud or misperception, with an exception for some independent external experts' fees that may be paid directly to them, provided their employer is informed. The amount of any payment must be estimated according to real work and represent a fair market value of the needs, negotiated in an arm's-length transaction.

We recommend that a single contract is signed by all partner organisations to avoid having multiple bi-partner and heterogeneous contracts for the PPC. The contract should clearly define the objectives of the project, the rational of the collaboration, the role, obligations, rights and responsibilities of each partner, the financial terms, the confidentiality rules, the data protection rules, the ownership and publications rights, rules for conflicts of interest

[15] http://www.icmje.org/; http://www.ismpp.org/gpp3
[16] http://www.eugdpr.org/

management, ethical considerations and all other necessary general information, such as the dates of the project start and end, termination terms etc.

During the ADVANCE workshop, the participating legal experts agreed that, at present, there are no hard legal barriers to developing vaccine B/R PPCs in Europe, as long as the considerations above are taken into account and agreed between organisations willing to collaborate..[6]

7.6 Summary of key steps for building governance for a PPC

ADVANCE recommends the use of a road map approach to building governance for a PPC. This should involve the consideration of the following questions to guide the choices:

1. What are the objective 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?

8. Conclusions

ADVANCE has provided a unique forum for open, frank and interactive discussions about their ideas and concerns on how organisations from the public and private sectors can collaborate and participate in future vaccine B/R monitoring projects in Europe. Although some PHIs can collaborate with private partners, others cannot. We need to accept and work with this heterogeneity in Europe, including the different attitudes to public-private interactions that are present among European PHIs, and other stakeholders in the vaccine benefit-risk field.

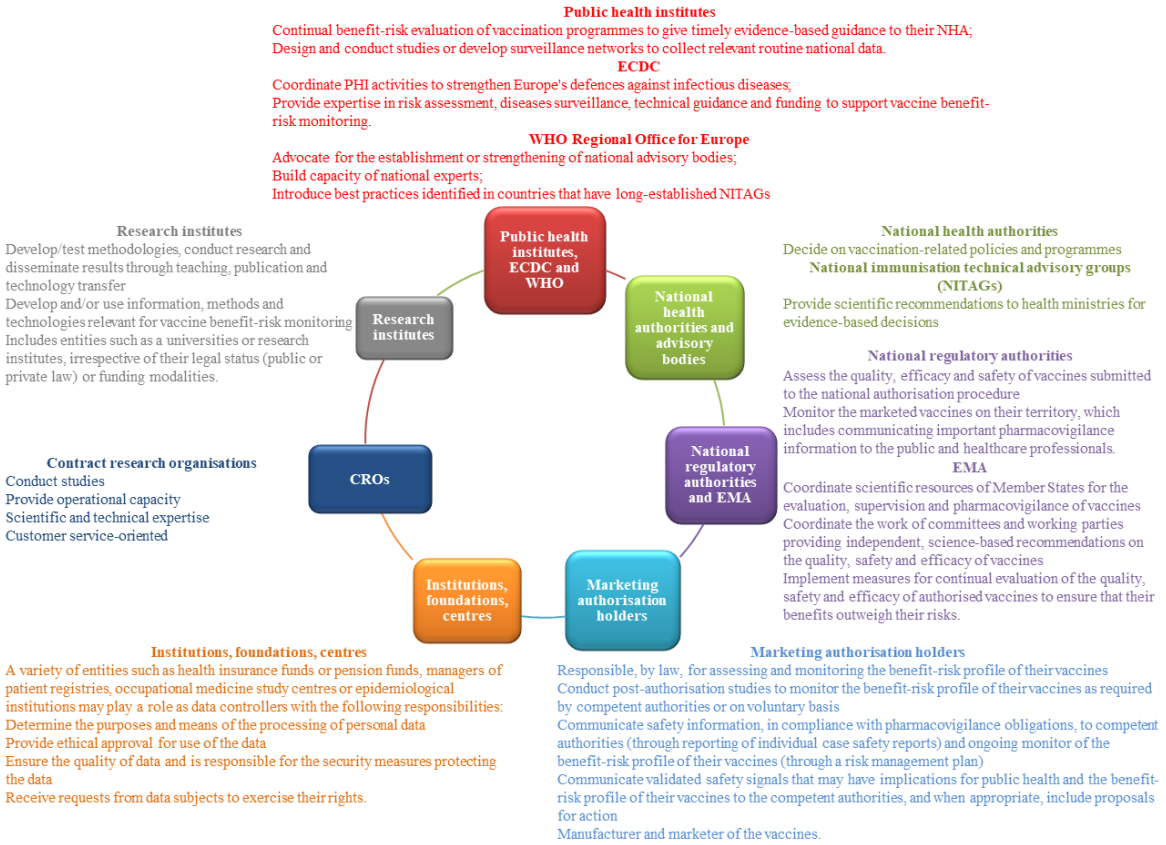
ADVANCE has proposed an approach for public-private collaboration based on best practice guidance which includes a Code of Conduct and governance guidance. There is no one-size-fits-all solution, and flexibility is essential to ensure that the governance structure fits the project objectives, while avoiding unnecessary complexity in the governance. For the future, accompanying flow charts and process documents could be developed and it would be useful

to provide a tool kit with materials that could be used by public and private stakeholders to formalise their collaborations, and in particular PPCs, in the post-ADVANCE era.

To move forward, we must be modest in our aims, and we have to accept that a PPC is not suitable for all projects and that it will not necessarily be accepted by all stakeholders. Trust is built step-by-step and we recommend to set-up collaborations between willing partners to demonstrate that it can work and what added-value could be obtained. Showing concrete success from PPCs may stimulate future PPCs. Trust takes time to be built but trust is fragile and can be quickly lost, so we must not try to run before we know how to walk. The ADVANCE basic governance guidance and recommendations can support organisations who want to implement vaccine B/R projects involving public and private organisations in Europe. In return, we expect that the governance guidance and recommendations will evolve through the lessons learnt from experiences of their use in real-life settings.

9. Appendices

Appendix 1: Key stakeholders in vaccine benefit-risk monitoring in Europe



Appendix 2: Integration of ADVANCE Code of Conduct in the governance of public-private collaborations

CORE TOPIC	PROVISIONS OF THE CODE OF CONDUCT Recommendations to be applied (**in bold**) and recommendations to be considered (*in italics*)	PROVISIONS OF THE GOVERNANCE GUIDANCE
1. Scientific integrity	**1. All study team members are qualified to fulfil their role.** **2. All study team members act in accordance with core values of honesty, accuracy and objectivity.** **3. Study team members adhere to IEA Good epidemiological practice and ISPE good pharmacoepidemiological practices.**	• The decision-making function can be attributed to one partner or can be attributed to a steering committee whose membership should reflect a balanced representation from the different public and private partners and include representatives from relevant civil society organisation(s). • Members of the technical/scientific advisory committee and of the audit committee will be independent experts from organisations not involved in the project, e.g. public health institutions, national regulatory authorities, and academia. Qualified scientists from organisations involved in the project (e.g., public health institutes or vaccine MAHs) can be involved if they have the expertise on specific aspects of the project, such as knowledge of the data source, the vaccination programme or the vaccine itself.
2. Scientific independence	**4. Study is conducted without undue influence of any financial, commercial, institutional or personal interest in a particular outcome of the study.** *5. Autonomy of members of study team for making scientific decisions in their organisation is documented.* **6. Scientific independence is safeguarded by clear and transparent roles and responsibilities, peer review process, transparency measures and disclosure of all funding sources**	• Processes for selection of the responsible party (responsible for the decision-making function) by an external organisation not involved in the project are proposed and described. • The decision making function will involve taking full responsibility for the project, and taking the lead on its strategic direction, allocation of funds and resources and making decisions related to the project. • The scientific and audit committees must include independent external experts chosen based on their specific expertise. The role of experts should be described in the agreement. Potential CoIs should be duly documented and their potential impact assessed. The compensation offered to experts should be justified by their tasks, workload and comply with their country's fair market value. • A trustee should be established to manage independently the financial aspects of the project, enabling transparent financial relationship between the contributing funders and the responsible party or the partners; to manage funds from multiple funders/partners centrally to ensure there is no earmarking of the funds; to ensure that funds are spent appropriately by implementing appropriate monitoring processes; and to provide appropriate records of financial accounts if required by auditors.

CORE TOPIC	PROVISIONS OF THE CODE OF CONDUCT Recommendations to be applied (**in bold**) and recommendations to be considered (*in italics*)	PROVISIONS OF THE GOVERNANCE GUIDANCE
3. Transparency	**7. Study is registered in a publicly accessible database before the start of data collection or extraction.** **8. Sources of funding are made public at the time of registration, in the protocol and in the presentation of results.** **9. Declarations of Interests (DoI) are made available at an early stage of the study, regularly updated and disclosed.** **10. All comments received on study protocol and results with impact on the study are documented.** *11. Final study report is uploaded in publicly accessible database where study is registered.* *12. After study completion, study information is made available from outside the study team in a collaborative approach.* *13. In case of primary data collection, participants in the study or their representatives may receive main study results and interpretation thereof.*	• The trustee responsible for the finance function should manage the budget with appropriate accounting and invoicing systems to ensure financial transparency and supporting independency; channel of funds are separately considered from the allocation of funds (done by the decision maker). • The trustee should provide reports on the traceability of the source(s) and beneficiary(ies) of funds to the decision maker. • The audit and quality control function should ensure transparency of the funding flow, transparency and proper documentation of the decision making process, that proper CoI declarations are recorded and that any related issues are escalated to the decision maker. • The decision-making function ensures effective communication between partners with regards to project progress and mediation between the partners to ensure consensus, if necessary. • Recommendations from the advisory functions should be clearly documented and any divergence in the final decision should be duly recorded and justified by the decision maker.
4. Conflict of interest	**14. Actual or potential conflicts of interest (and perceptions thereof) are addressed at the planning phase of the study. Research contract includes a description of the management of conflicts of interest. All DoI are made publicly available.** *15. A standard form is used to declare all interest that may lead to conflicts.*	• The audit and quality control function should assess, manage and mitigate potential conflicts of interest that may occur in the project, ensure that proper declarations are recorded and that any related issues are escalated to the decision maker. • A stepwise approach for the management of the risk associated with conflicts of interest in collaborative public-private projects should be used, such as the risk management guidance proposed by WHO.

CORE TOPIC	PROVISIONS OF THE CODE OF CONDUCT Recommendations to be applied (**in bold**) and recommendations to be considered (*in italics*)	PROVISIONS OF THE GOVERNANCE GUIDANCE
5. Study protocol	**16. A study protocol is drafted as one of the first step in any research projects.** **17. Study protocol is developed with persons with relevant expertise.** **18. The process for reaching an agreement on the design options of the study is agreed beforehand.** **19. Protocol includes a section with ethical considerations involved and information on funding, affiliations, potential conflicts of interest, data protection and incentives to subject. Protocol is approved by relevant research ethics committee.** **20. Protocol includes description of each party to study design, protocol writing and work programme.** **21. Regulatory obligations and recommendations are described.** *22. Detailed draft protocol undergoes independent scientific review.* *23. Protocol is registered in publicly accessible database before the start of data collection.* **24. Changes to the protocol that may affect the interpretation of the study are identifiable and reported in the study report.** **25. Key statistical analyses are described in the protocol.**	• The advisory function should be involved in reviewing and providing advice on the protocol. • The decision-making function should be responsibility for seeking advice from other parties or committees for technical, scientific, quality and compliance considerations.
6. Study report	**26. Set of principles are followed for reporting results including documentation of important safety concerns and deviations from protocol or statistical analysis plan, sources affecting data quality, strengths and limitations, and sources of funding.** **27. STROBE statement and internationally-agreed guidelines are consulted when analysing and reporting data.** *28. Draft study report undergoes independent scientific review.* *29. Study report or summary of the results is included in the publicly accessible database.*	• The advisory function should be involved in reviewing and providing advice on data interpretation, study report, scientific communication and publications.

CORE TOPIC	PROVISIONS OF THE CODE OF CONDUCT Recommendations to be applied (**in bold**) and recommendations to be considered (*in italics*)	PROVISIONS OF THE GOVERNANCE GUIDANCE
7. Publication	**30. All study results are made publicly available. Authorship of publications follows the rules of ICMJE.** **31. Research contract allows the principal investigators and relevant study team members to publish study results independently from the funding or data source. The study requester/funder may provide comments.** *32. Preliminary or partial results of discontinued study are reported and identified as such.* **33. Procedures are in place to rapidly inform regulatory and public health authorities of study results, independently from submission of a manuscript.**	• The decision-making function will be responsible for managing external communication and advocacy related to the project and ensuring project results are published and communicated. • Publication rights should be discussed before the project is started and should be described in the contract. Any publication should comply with international recommendations for the publication of scientific results and authorships; partners should not deviate from these rules in any way.
8. Subject privacy	**34. Privacy of study subjects in relation to personal data is core principle of any medical research.** **35. In case where personal data are collected, the applicable legislation is followed.**	• The audit and quality control function will be responsible for ensuring compliance of the handling of personal data with applicable national and international laws and regulations concerning data security and data protection.
9. Sharing of study data	*36. There is an open and collaborative approach to sharing study data with persons from outside the study team.* *37. Data are shared only after the study report is finalised.* **38. Sharing of study data is based on a written request specifying the ground of the request. The study team verifies the compliance of the request with the data protection legislation.** **39. Requests for data sharing are justified based on public health interest.** *40. Study team or delegated committee takes the decision to share study data.* **41. Analyses performed with shared data follow the provisions of the ADVANCE Code of Conduct.**	• The implementation function should ensure that legal rights for data access are followed. • The transfer of personal data is strictly regulated and partners cannot request more than what is allowed by the law. • Personal data are protected and the potential user or entity that can access these personal data may be controlled and audited.

CORE TOPIC	PROVISIONS OF THE CODE OF CONDUCT Recommendations to be applied (**in bold**) and recommendations to be considered (*in italics*)	PROVISIONS OF THE GOVERNANCE GUIDANCE
10. Research contract	**42. Research contract does not lead investigators, directly or indirectly, to act against the principles of the Helsinki Declaration or applicable legal or regulatory obligations.** **43. Clarity and transparency are key elements of research contract.** *44. Unique multiparty contract is preferred in cases where several parties interact.* *45. Research contracts indicate that the study will follow the ADVANCE Code of Conduct and provide core information.*	• The decision-making function has the responsibility for scientific, ethical, legal and compliance aspects of the project**.** • A list of information that can be included in the PPC contract has been identified.