



**Accelerated Development of VAccine beNefit-risk
Collaboration in Europe**

Grant Agreement n°115557

**Good Practice Guidance
Module 2: Governance models**

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

**Deliverable 1.10 - Final conceptual models
for public-private interaction**

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	Good Practice Guidance – Module 2: Governance models (D1.10)		
	WP1. Best practice and code of conduct for benefit-risk monitoring vaccines		Version: V5
	Author(s): Laurence Torcel-Pagnon, Cédric Mahé, Xavier Kurz, Vincent Bauchau, Myint Tin Tin Htar, Anne Charrat, François Simondon, Patrick Mahy and Tyra Grove Krause for the working group WG3	Security: PU	2/47

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Description of the deliverable	This deliverable aims to propose governance principles and models that might be used as recommendations to implement collaborations or partnerships for vaccine benefit-risk assessment in Europe.
Key words	Governance, multi-stakeholders public-private initiatives/interactions, collaborations, partnerships.


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Laurence Torcel-Pagnon Myint Tin Tin Htar Cédric Mahé	27 th January 2015	1.1	Preliminary draft
Miriam Sturkenboom	24 th February 2015	1.2	Review and comments
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Cédric Mahé Anne Charrat			content and theoretical governance model, integration of the scenario following presentation at the GAM in September
Georgina Tzanakaki Patrick Mahy	7 December 2015	3	Review and comments
Laurence Torcel-Pagnon Anne Charrat	12 January 2016	4	Update following WP1 Workshop in December 2015
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Patrick Mahy José van Boxmeer Marianne van der Sande Mendel Haag Alison Cave	19 April -23 May 2016	4	WP1 review and comments

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Laurence Torcel-Pagnon Xavier Kurz Cédric Mahé Vincent Bauchau	17 October 2016	5	Integration of comments and finalisation of the report

Participants of the ADVANCE Consortium are referred to herein according to the following codes:


- **AUH.** Aarhus Universitetshospital (Denmark)
- **AEMPS.** Agencia Española de Medicamentos y Productos Sanitarios (Spain)
- **ASLCR.** Azienda Sanitaria Locale della Provincia di Cremona (Italy)
- **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) - Coordinator
- **GSK.** GlaxoSmithKline Biologicals, S.A. (Belgium) – EFPIA Coordinator
- **KI.** Karolinska Institutet (Sweden)
- **LSHTM.** London School of Hygiene and Tropical Medicine (United Kingdom)
- **OU.** The Open University (United Kingdom)
- **MHRA.** Medicines and Healthcare products Regulatory Agency (United Kingdom)
- **NOVARTIS.** Novartis Pharma AG (Switzerland)
- **PEDIANET.** Società Servizi Telematici SRL (Italy)
- **PFIZER.** Pfizer Limited (United Kingdom)
- **P95.** P95 (Belgium)
- **RCGP.** Royal College of General Practitioners (United Kingdom)
- **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu * National Institute for Public Health and the Environment (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)

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- **UNIBAS.** Universitaet Basel (Switzerland) - **Managing entity of the IMI JU funding**
 - **UTA.** Tampereen Yliopisto (Finland)
 - **WIV-ISP.** Institut Scientifique de Santé Publique (Belgium)
- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ADVANCE project (115557).
 - **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
 - **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
 - **Consortium.** The ADVANCE Consortium, comprising the above-mentioned legal entities.
 - **Project Agreement.** Agreement concluded amongst ADVANCE participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

List of abbreviations:

- B/R: Benefits-risks
- CoI: Conflict of Interest
- CoC: Code of Conduct
- CRO: Contract Research Organisation
- CV: Curriculum Vitae
- EC: European Commission
- ENCePP: European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
- EU: European Union
- MAH: Marketing Authorisation Holder
- NRA: National regulatory Authority
- PBRER: Periodic Benefit-Risk Evaluation Report
- PHI: Public Health Institute
- PoC: Proof of Concept
- PRAC: Pharmacovigilance Risk Assessment Committee
- RMP: Risk Management Plan
- SME: Small and Medium Size Enterprise


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EXECUTIVE SUMMARY

The pandemic influenza season and the new pharmacovigilance legislation have changed the paradigm in Europe on how vaccines should be monitored in post marketing settings and how public and private stakeholders should interact to maintain confidence in immunisations.

ADVANCE, an IMI project, aims to establish a framework that could provide rapidly robust post marketing data on vaccines Benefits-Risks (B/R) to support decision making in Europe. This consortium with public-private stakeholders coming from Public Health Institutes, ECDC, National Health Authorities, EMA, Academia, CRO-SME and Vaccines Manufacturers, provides a unique forum where key players in vaccines work together to develop and propose common rules and governance structures for public-private interactions.

This report presents the ADVANCE guidance on governance developed to integrate both complementary and synergistic roles of public and private stakeholders involved in vaccines B/R monitoring. It describes the basics of good governance with clarifications of terms and structure, as well as the specific European environment for vaccines. Governance models and recommendations were developed to ensure transparent, acceptable and ethical public-private interactions. The ambition of this guidance is to facilitate implementation of good principles into the everyday practice for future collaborative projects.

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1. PREFACE

The pandemic influenza vaccines (2009-2010) has changed the paradigm in Europe on how vaccines should be monitored in post marketing settings and how public health authorities and regulators could maintain public confidence in immunisations. With the new pharmacovigilance legislation (that came into force in Europe in 2012), Marketing Authorisation Holders have been requested to include post-authorisation safety and effectiveness studies in the risk management plan of their vaccines. Monitoring vaccines benefits-risks (B/R) is therefore a responsibility for both public and private stakeholders. Joining their efforts through collaborative projects with transparent governance may be of great added value in similar crisis situations and may also support the utilisation and integration of vaccine real life data across countries.

ADVANCE is a unique forum where 45 partners from Public Health Institutes, ECDC, National Health Authorities, EMA, Academia, CRO-SME and Vaccines Manufacturers work together to establish a framework that could provide rapidly robust data on vaccine benefits and risks to support decision making in Europe. ADVANCE is at the forefront of efforts to propose common rules and governance structures for public-private interactions, to profile secondary use of large healthcare and other databases and develop methods for integrated analysis for B/R monitoring in Europe. The consortium also provides a forum where stakeholders can compare their views, discuss answers to common problems and identify good practice.


Some guidelines for governance in public-private interactions already exist. But most of them were developed for basic science projects, product development, defence, building public facilities, or are intended to manage broader complex partnership such as The Global Fund or GAVI. None of them fulfilled the needs of governance models and guidance to implement collaborative public-private projects for post-marketing B/R monitoring of vaccines in Europe.

Our starting point has been that important aspects of governance are generally not well known by researchers devoting their time on vaccines B/R monitoring. Discussions within the consortium indeed revealed that many stakeholders share common concerns about their roles and responsibilities in public-private projects, the level of transparency required and the level of trust within public, and are not very familiar with principles of governance.

An ADVANCE working group with representatives from key stakeholders (nominated in the Document History section above) has therefore been established to work jointly on proposals for governance models and guidance for public-private projects on B/R monitoring of vaccines. This guidance has been developed in open discussions and fruitful exchanges between stakeholders during workshops and ADVANCE General Assembly meetings with a broader representation of ADVANCE partners. However the guidance and recommendations proposed herein do not necessarily reflect the official view of the respective institutions and organisations.

This report presents the views of the ADVANCE working group on the implementation of a transparent and trusted collaborative public-private project for vaccines B/R monitoring in Europe. This report also describes the basics of good governance with clarifications of terms and structure, as well as the specific European environment for vaccines.

Our ambition is that this guidance will facilitate implementation of good principles of governance into the everyday practice. It is hoped that these governance standards will provide an agreed and accepted format to establish public-private interactions and therefore will not have to be developed and negotiated for each project.

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The ADVANCE guidance on governance has been developed to integrate both complementary and synergistic roles of public and private stakeholders involved in vaccines B/R monitoring. Contribution from project partners is envisioned to go beyond mere provision of funds, data, facilities or expertise. The Governance models and recommendations emphasize the added value of public-private interactions, facilitate transparent and ethical collaborations between stakeholders involved in a project and is thereby expected to support public confidence in its results.

2. GOVERNANCE BASICS

2.1 Clarification of terms

Several terms are used in the Governance field depending of the area of interest, such as Public facilities, Environment or Defence. We have chosen to start with simple terms and definitions that will be used throughout this report.

Definitions related to scientific independence, scientific integrity, transparency and conflict of interest are already provided in the ADVANCE Code of Conduct (Good Practice Guidance, Module 1) and used accordingly here throughout this document.

Stakeholder: organisation (institution, authority, foundation, research academy, company...) taking part in the project/initiative and having an interest in the project results.

Public-private interaction: initiative where public and private stakeholders are engaged.

Governance: processes of interaction and decision-making among the stakeholders involved in the project.


Contributor: organisation that is contributing to the project providing resources, funds (in which case it is called a **contributing funder**), expertise, data, workforce or any other contribution.

Committee: group of stakeholders representatives in charge of a dedicated governance function in the project.

Trustee: organisation that holds and administers property or assets for the benefit of a third party. Trustee is an independent legal entity without any scientific or financial interest in the project and having specific skills and rights to channel funds in a transparent way between the stakeholders. The trustee is not the funder itself.


Responsible party: single organisation that endorses the decision making function.

Steering Committee: governance body with representatives from several stakeholders for shared decision making.

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In this document, two models of interactions have been considered depending who is endorsing the legal responsibility of the project and is therefore considered as the decision maker.

	Collaboration	Partnership
Objectives	Joint interest, more often study specific and time limited	Common vision and mission with shared goals, generally for longer terms initiatives with boarder objectives
Roles and responsibilities	Roles are distributed between stakeholders	Roles, resources and financial investments are shared between stakeholders
Legal representative	An organisation is legally responsible and accountable for the project	A governance body is created to establish shared decision making between several stakeholders. All partners have the right and the responsibility to participate and will be affected by the benefits and other consequences arising from the partnership.
Decision making	Responsible party	Steering Committee

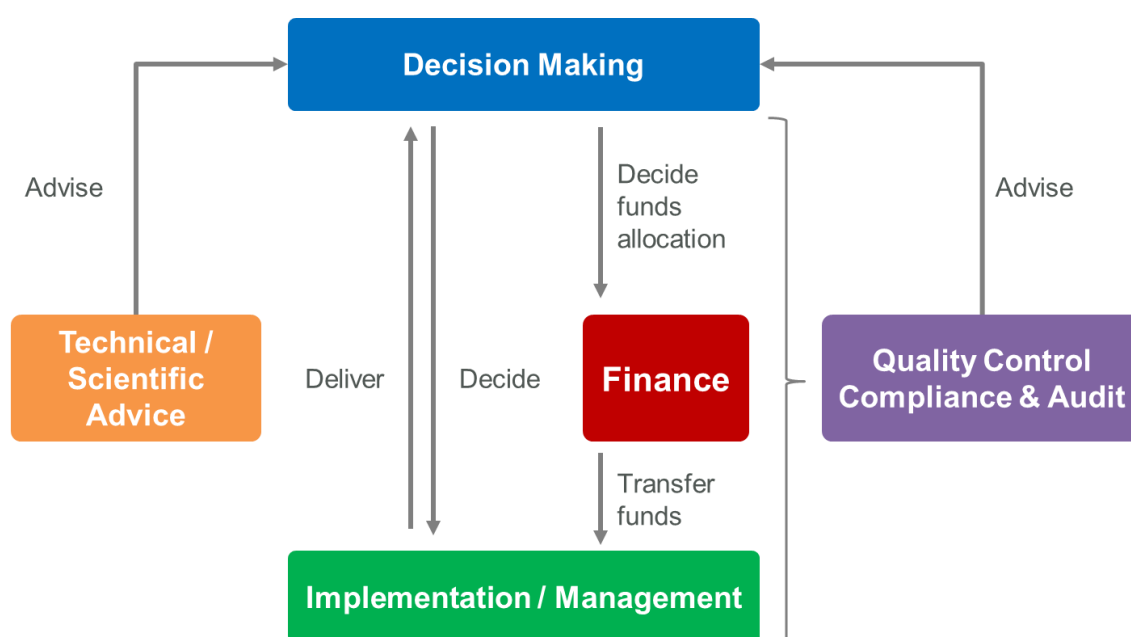
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2.2 Structure and core functions


The governance structure is articulated around five core functions aiming to define the roles and responsibilities of the stakeholders and their interactions (Figure 1).

Those functions may be either distributed between stakeholders or incarnated in a governance body (committee).


Figure 1. Governance structure diagram by functions



Five core functions	Roles and responsibilities
Decision-making assumes ultimate responsibility for the project, leading on its strategic direction, allocating funds and resources and making decisions for the project	<ul style="list-style-type: none"> ○ Having the responsibility for scientific, ethical, legal and compliance aspects of the project; ○ Ensuring that all tasks are assigned for the project based on the agreement between parties; ○ Ensuring effective communication between parties with regards to project progress and mediating between the parties if needed to ensure consensus; ○ Governing the overall project; endorsing the work plan, following up high-level progress in each of the critical areas of the project; taking when necessary the appropriate corrective actions and performing contingency plans and risk management for the project; ○ Allocating and reassigning (if necessary) budget and resources to keep the project aligned with the objective; ○ Seeking advice from other parties or committees for technical, scientific, quality and compliance

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	<ul style="list-style-type: none"> considerations; Agreeing the project deliverables, ensuring that milestones are fulfilled with an appropriate quality level and preparing final project assessment; Managing external communication and advocacy related to the project and ensuring project results are published and communicated.
Technical/scientific advice provides recommendations for technical, scientific and related ethical aspects of the project	<ul style="list-style-type: none"> Contributing to, reviewing and advising on the scientific deliverables such as the research plan, protocol, analysis, interpretations, report, scientific communication and publications; Overseeing technical, scientific and related ethical aspects of the project Advising the decision maker on technical and scientific topics providing specific recommendations. Those recommendations should be clearly documented and any divergence in the final decision should be duly recorded and justified by the decision maker.
Implementation/execution implements and executes the project under the oversight of the decision maker	<ul style="list-style-type: none"> Managing the day-to-day operational aspects of the project; ensuring technical, legal (e.g. contract development) and administrative (e.g. ethics and data protection related submissions) tasks under the decision maker's authority and liaising with the project stakeholders as required; Producing the scientific deliverables such as research plan, protocol, statistical analysis plan, report, scientific communication and publications; Ensuring legal rights for data access; Ensuring project tasks are done directly by stakeholders or through appropriate subcontractors; Managing the communication between the parties; Ensuring that all persons involved in the project implementation are well informed and qualified; Reporting deliverables and progress to the decision maker and suggesting possible corrective actions (e.g. protocol amendment); reports and status should be clearly documented and shared between stakeholders for transparency purpose.
Quality control and audit controls, audits and advises on governance and quality of the project	<ul style="list-style-type: none"> Auditing the governance: ensuring that governance principles and rules are well followed within the project: <ul style="list-style-type: none"> Transparency of the funding flow; Transparency and proper documentation of the decision making process; Assessment of the potential conflicts of interest which may occur in the project; ensuring that proper declarations are recorded; escalating any related issues to the decision maker; Ensuring quality control and corresponding auditing: <ul style="list-style-type: none"> Alignment with the relevant guidelines,

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	<ul style="list-style-type: none"> national and international standards and requirements; Alignment of (personal) data handling with applicable national and international standards of data security and data protection; Overseeing the compliance of the project Reporting findings to the decision maker and giving advise with recommendations and proposed action plan if needed. Those findings and recommendations should be clearly documented; any deviation in the final decision should be duly recorded and justified by the decision maker.
Finance manages funds devoted to the project	<ul style="list-style-type: none"> Managing the budget with appropriate accounting and invoicing to ensure financial transparency and supporting independency; channel of funds are separately considered from the allocation of funds (done by the decision maker) Reporting on traceability of the source and beneficiary of funds to the decision maker.

The core function is Decision-making which represents the "raison d'être" and embodies the objectives of the various stakeholders.


In the context of public-private interactions, technical/scientific advice and quality control and audit are key functions to be considered to guarantee the scientific relevance, acceptability, ethics and transparency of the project. Therefore, these functions should be independent from both the decision making and implementation and management processes.

3. THE CONTEXT OF VACCINES B/R MONITORING

3.1 Background

Vaccination is acknowledged as one of the most effective and widely used public health interventions, whose benefits for individuals and the community have been demonstrated. Vaccines are however complex biological products that may include multiple antigens, live organisms, adjuvants, preservatives and other excipients. Each of these components may have safety and effectiveness implications.

At the time of the marketing authorisation for a new vaccine, its quality, efficacy and safety must have been demonstrated. However, there may be limited data concerning adverse reactions that are delayed or too rare to be detected in randomised clinical trials or that appear in special population groups. Robust systems and procedures must therefore be in place to continuously monitor quality, safety and effectiveness of vaccines after their authorisation and marketing. At the EU level, such post-authorisation evaluation of the benefit- risk profile of vaccines is an ongoing process under the responsibility of marketing authorisation holders and regulatory authorities. As part of their mandate, Public Health Authorities continuously evaluate benefits and risks of any intervention, including

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vaccinations, offered to their populations. Post-authorisation safety studies may also be required by regulatory authorities in order to identify, characterise or quantify a safety hazard, confirm the safety profile of the vaccine, or measure the effectiveness of risk management measures.


For several reasons, routine benefit-risk monitoring in a post-marketing environment is challenging for vaccines. These reasons include:

- The benefit-risk balance for vaccines depends on many population level factors which cannot be considered in isolation. It includes: the incidence of the vaccine preventable disease, its geographical distribution, sometimes the seasonal characteristics, the risk of transmission in the target population, the proportion of infected persons with a clinical manifestation, the severity, the vaccine coverage, indirect protection and concomitant vaccinations. These demographic and geographic related factors need to be taken into account when estimating the benefit and risk of vaccines and may require data collection from several countries.
- Data need to be collected from different sources (electronic health records, vaccination registries, surveillance data ...). For effectiveness studies requiring laboratory confirmation of the disease or strain of the infectious agent, primary data collection may be the only source of reliable information.
- Robust systems and procedures need to be in place to mount a rapid response, (in the event of a disease outbreak or a vaccine safety concern) ; an immediate action and communication may be key to not endanger public health and public trust.

Timely vaccine benefit-risk monitoring studies may therefore only be possible or benefit significantly from pre-established collaborations between key players involved in data collection and management on vaccine exposure, safety and effectiveness.

3.2 Key players

There are several key players in the monitoring of vaccines B/R with different roles, mandates and obligations (Figure 2).

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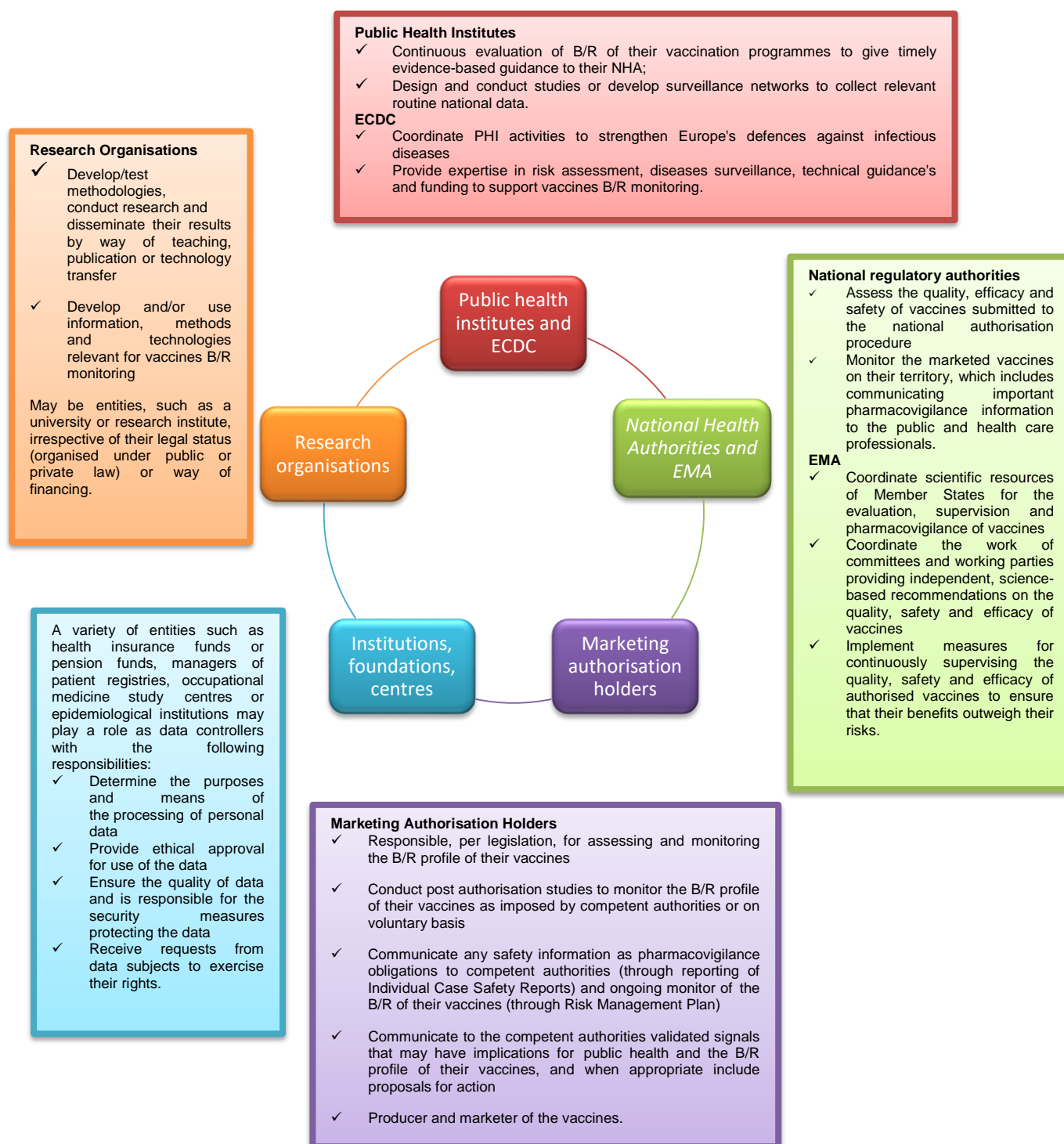



Figure 2. Key players in vaccines B/R monitoring

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3.3 Added value of interactions

The main motivations for public and private interaction in monitoring vaccines B/R are presented below (Figure 3):

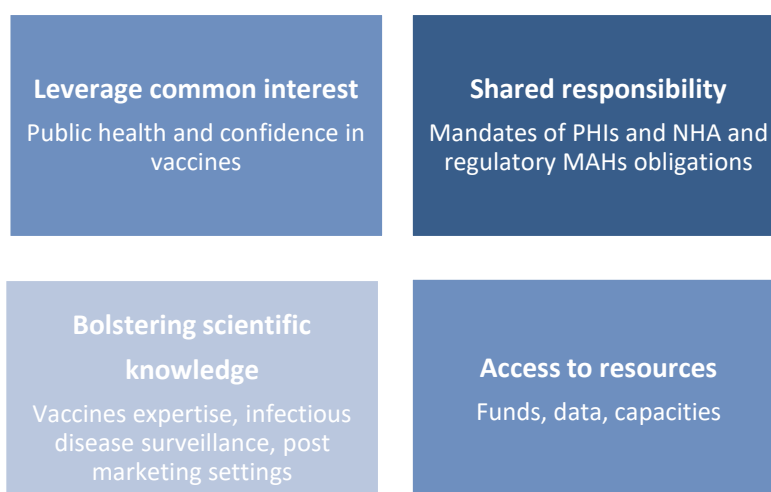



Figure 3: Added value of public-private interactions

Leverage common interest: Evaluation and update of the B/R profile of vaccines and vaccination programmes are activities shared between public health and regulatory authorities and MAHs Joint monitoring of vaccines B/R can support the responsibilities of all parties, which can contribute to improve public health and increase public confidence in vaccines. Having access to large databases of the European population with information on vaccination information can allow all investigators (PHIs/NRA/MAHs) to study, observe and generate more robust results on the safety and effectiveness of the vaccines and/or of the vaccination campaigns that were launched by national authorities.

Shared responsibility: National public health institutes (PHIs) have the responsibility to evaluate the benefits and risks of their vaccination programmes and national regulatory authorities (NRAs) are responsible for monitoring the quality, safety and efficacy of marketed vaccines on their territory. Because routine vaccine B/R evaluation has become part of their regulatory requirements, MAHs need such data to fulfil their obligations, but equally important, to allow the development of safer and more effective vaccines (which will ultimately increase their income).

Access to resources: Significant investments are needed to enable timely and robust integrated post-marketing benefit-risk analysis of a specific vaccine. These investments need to be made prior to any critical situation to ensure that results can be available in near-real time. As there are competing priorities in public health infectious disease control, public funding may be insufficient to develop and maintain such a system. Academic partners often have little structural funding and need to obtain funding from external parties (public or private) to be able to initiate projects. Therefore, interactions with private partners who have the knowledge of vaccines development and may have access to dedicated funding for such post-marketing surveillance can be an added value for public partners.

In parallel, data relevant for vaccines B/R are more often owned by the public sector (electronic repositories of routine data, sentinel networks or laboratory data). Therefore interactions between public and private sectors have added value for MAHs to increase the required capacity as well as to create synergies beyond the different partners' capacities using existing structure/network/databases, to link and to pool data coming from various sources through different countries and ultimately to provide better B/R estimates.

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Bolstering scientific knowledge: Bringing together professional and personal skills of individuals from various organisations with different scientific expertise and experience is an added value for research projects. In the context of vaccines B/R monitoring, expertise/experience in research on vaccines, vaccination programmes, related infectious diseases and project design, conduct and analysis is a key element of consideration. Public-private interactions may facilitate scientific brainstorming and discussion for the benefits of the research project. This may lead to studies of better quality providing evidence on vaccines and vaccination programmes.

3.4 Major stakeholders constraints

Public-private interactions in the context of vaccines B/R monitoring nevertheless raise challenges linked to stakeholders constraints (Figure 4):

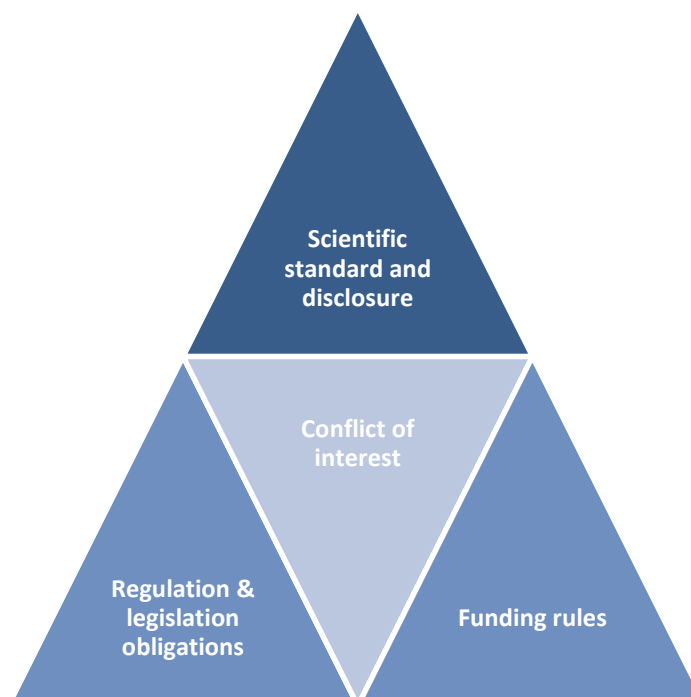



Figure 4: Major stakeholders constraints

Scientific standard and disclosure: Because MAHs are highly regulated and have financial interests, they must have rigorous quality control and auditing processes in place. And because of the disclosure regulation and the potential impact of any results, MAHs are limited in performing exploratory analysis in comparison to for example research organisations who may wish to test designs and methods. On the other hand, PHIs may perceive direct collaboration with MAHs' scientists as a threat to their scientific credibility.

Conflict of interest: A conflict of interest is a situation in which a person or organisation involved in a research project has a professional, personal or organisational interest sufficient to influence the

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objective exercise of his/her/its judgment towards any activity of the project (refer to ADVANCE Code of Conduct). Conflicts of interest represent a major risk area in both the public and private sectors. In the recent years, there has been an increased awareness on declaration of such interests to enhance transparency

In post marketing settings, conflicts of interest represent an important issue for public authorities in charge of the monitoring of vaccines and vaccination programmes and of taking decisions in the interest of public health. Interactions with MAHs may lead to a perception among the general public that their research is biased, aiming at selling vaccines, rather than serving public health. This perception may be stronger when funding for the project is provided by MAHs and when they are also involved in scientific decision making roles. For research organisations, conflicts of interest may be linked to the search of funds for their sustainability. While conflicts of interest and their orientation are obvious for MAHs, it can be less clear for public health sector since it could be more political.

Regulation and legislation obligations: PHI constraints vary among different organisations. For some PHIs, there are explicit legal constraints limiting the scope of public-private interactions. For others, there is political support to develop public-private interactions. Such (lack of) support could change with changing legislation, financial constraints and political or societal developments.

MAHs must comply with the requirements of the EU legislation during the lifecycle of their vaccines. Companies must produce, maintain and submit a Risk Management Plan (RMP) to the competent authority at the time of the authorisation and continuously update it. The RMP aims to ensure that the benefits of a particular vaccine exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. MAHs must collect and evaluate safety reports and submit Periodic Safety update reports (PSURs) at defined time points to summarize data on the benefits and risks of their vaccine and include the results of all studies carried out with this vaccine. Post-authorisation studies (PAS) conducted by MAHs may be either imposed by competent authorities or based on their own initiative in line with their risk-management plan. When a PAS is initiated, managed or financed by a MAH, the MAH has to comply with general guidance on transparency, scientific standards and quality standards including the education, training and experience of the persons involved in the project, the reporting of adverse reactions, the storage and availability of the analytical dataset and statistical programmes for audit and inspection and the publication of the project results. These obligations imply a high degree of quality and documentation to MAHs who have developed strict quality assurance systems to meet these requirements


Funding rules: Pharmaceutical companies have to duly justify and track allocation of their funds to comply with their objectives and legal obligations of transparency and with their internal financial reporting rules. The Disclosure Code, edited in July 2014 by the European Federation of Pharmaceutical Industries and Associations (EFPIA), is an illustration of the current context to be considered for funding of research. Such disclosure is already in place at national level and binding by law in France and Portugal. This code aims to make transfer of values to health care professionals and organisations (HCPs/ HCOs) transparent to, and available for consultation by the general public. The objective is to prevent undue relationship between pharmaceutical companies and HCPs/HCOs, as well as to demonstrate to general public that all value transfers should have a scientific and genuine purpose for the benefit of the overall community.

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3.5 Governance triggers and challenges

Public-private interactions have specific challenges and there can be shifting and diverting opinions among stakeholders on the political or societal desirability of interaction between public and private partners. For each partner, the added benefits need to outweigh the additional efforts and risks needed to achieve a successful interaction. Therefore, it is important that each partner has a clear vision of the expected added value, and on the risks and challenges of such an interaction in view of its own mission. At the same time, each partner in the interaction should be aware of, understand and respect the perspectives of the other partner(s). It should be acknowledged that in some situations, stakeholders may decide to not pursue with a collaboration/partnership if such model has not of big added value for the stakeholders.

Collaborative projects with different stakeholders require additional time and energy to create a common language and mutual understanding of strengths and limitations, compared to projects which can be done by a single party. Involvement of a great number of different actors may therefore slow the processes. Collaborators or partners may lose commitment if interactions become very complex and technical, or where the delay between the emergence of relevant public health questions and the project conduct may become too long. An appropriate governance model needs to be able to generate the added values and mitigate the constraints of the interaction for all involved partners as discussed above as much as possible.

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Our governance proposals are articulated around principles which aim to address the following challenges:

- Engage collaboratively stakeholders as to maximise added values and to mitigate constraints
- Ensure transparency in the decision making process
- Identify, manage and mitigate personal and organisational conflicts of interest
- Ensure scientific relevance, ethic and compliance/adherence for the public health benefit
- Keep it as simple as possible for an rapid implementation and efficient execution.


4. GOVERNANCE PROPOSALS

4.1 Guiding Principles

Complementing the general principles described in the Code of Conduct for scientists involved in collaboration or partnerships, governance models should reflect the following key principles:

Efficiency

- Formal multi-stakeholder initiatives are demanding and time intensive. Careful consideration should be given to the most relevant form of interaction for a given project (study or programme of studies);
- The public health gains should be commensurate with the time and expense to establish and maintain the public-private relationship. Irrespective of the chosen model for interactions, the governance structure should be transparent, acceptable, as simple as possible and appropriately sized to ensure efficiency;
- A clear understanding of why the partners are coming together and why their objectives cannot be achieved at all and/or as efficiently through other mechanisms should be addressed at the earliest stage;
- Clear roles and responsibilities and decision making rules should be established and accepted upfront, leaving no room for multiple interpretations; agreement should be established between parties to formalise the terms and conditions of the interaction;
- In partnership, governance processes and decisions should focus on achieving the objectives of the interaction rather than seeking compromise between the interests of different stakeholders; these processes should welcome a variety of inputs but may not require full consensus on the final decision which has to be made in a timely manner;


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Equity

- The common interest of the stakeholders, 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;
- In partnership, a fair balance of the decision making should be established between partners participating in the Steering committee;
- The different perspectives of the stakeholders should be considered as an objective of the interaction and governance structure should be to ensure that all stakeholders' point of views can be heard especially in partnership.

Transparency

- Participating organisations should ensure that roles and responsibilities are performed by people with relevant position, knowledge, motivation, skills and resources including time available for the project; This will be enhanced if participating organisations develop and promote the scientific autonomy of their employees and reflect these aspects in their internal governance policies and processes;
- Continuous monitoring of compliance to CoC and good practices during the implementation and conduct of the project until the end of the collaboration or partnership should minimise the risk of CoI and support scientific autonomy;
- All decisions, key communications and minutes from the different committees meetings should be documented; this will facilitate audit and monitoring of the compliance. A communication plan should be adopted to prevent the perception of conflicts of interest and pre-define escalation processes in case of issue;
- Inclusion of representatives from patients or HCP associations as observers in the steering committee body could also support transparency;
- Policies related to compliance with good practices, prevention of conflict of interest and scientific autonomy (as defined in the CoC) should be shared between stakeholders. Specific training to support compliance with the ADVANCE Code of Conduct and good practices aiming at preventing conflicts of interest and supporting scientific autonomy, and on the bioethical aspects of the research should be provided.

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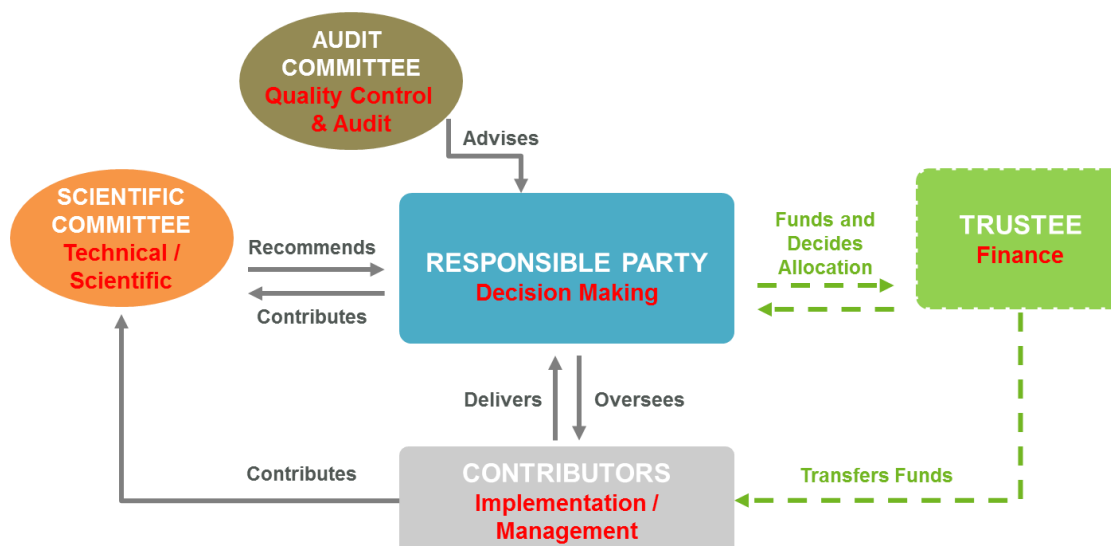
4.2 Governance models

This chapter describes and illustrates models of governance with various levels of complexity. It explains how the core governance functions are distributed among the different parties. None of these models of interactions are considered superior to the others. The choice of the model depends upon the vision and mission of the project, the typology and contribution of stakeholders and how they would like (or are able) to collaborate to answer to the public health question(s). The proposed models have been developed to integrate both complementary and synergistic roles of public and private stakeholders in vaccines B/R monitoring. Contribution from project partners has been envisioned to go beyond mere provisions of funds, data facilities or expertise.


Legend for the models

Parties are defined based on their institutional roles in the governance (in white fonts). Square boxes represent stakeholders and round boxes represent governance bodies. Stakeholders and bodies required for the governance are indicated in white fonts. Entities specified in a box with solid lines are essential, those specified in a box with dotted lines are optional. The core governance functions are indicated in red fonts.

Model 1: Collaboration self-funded by the Responsible Party



The Decision-Making function is ensured by the Responsible Party, a unique stakeholder, who is also the funder and has project oversight. The Contributor(s) participates to the project through different manners such as provision and analysis of data.

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The Scientific Committee should be composed of representatives from the Responsible Party, the Contributors and must include independent external experts.

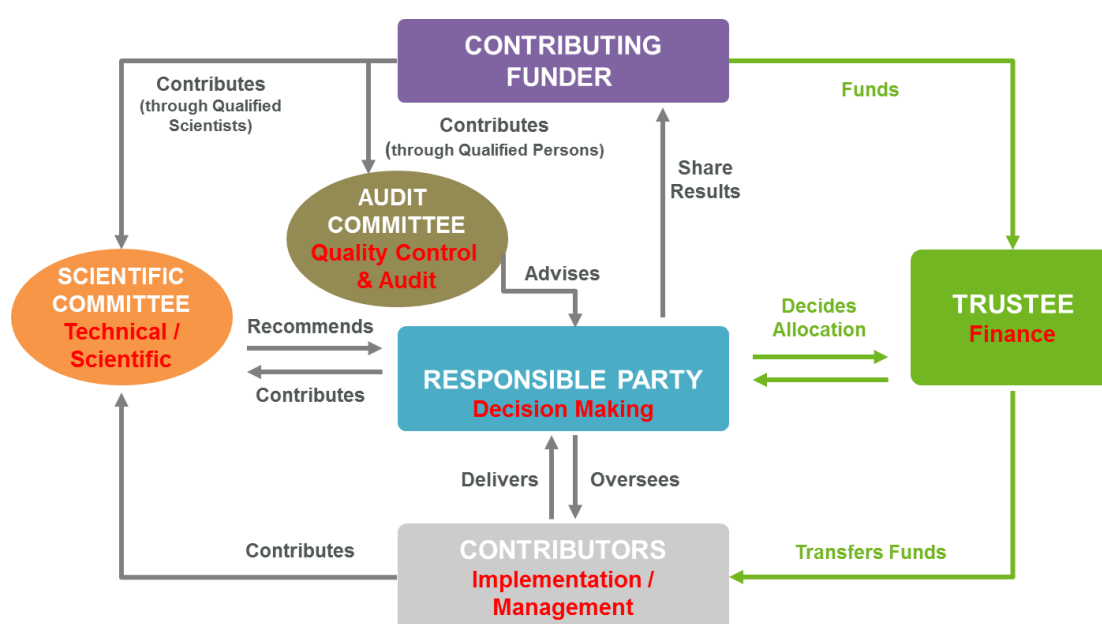
The Audit Committee could be either a body exclusively constituted by independent experts coming from an organisation which is contributing neither in the decision making nor in the implementation/management functions, or a body with representatives from the Responsible Party with independent external experts. In that last case, representatives from the Responsible Party should be considered by their position and function as independent from those involved in the Decision making process.


In this type of collaboration, a trustee is not essential but can be used to manage the financial assets especially in case of involvement of several contributors or when funds need to be earmarked and/or traceable.

From a legal point of view, the Responsible Party and the Contributor(s) shall sign a contractual agreement to set the terms and conditions. Independent external experts participating in the Scientific Committee or the Audit Committee shall be part of the contractual agreement.

Rights of use of the data and/or co-ownership of the results and rights to the publication of those results (in line with authorship guidelines) should be discussed upfront between the parties and mutually agreed between the Responsible Party and the Contributors.

Model 2: Collaboration with Contributing Funder(s)



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The decision making function is ensured by the Responsible Party, a unique stakeholder, who has project oversight and receives funding from other parties (the Contributing Funder(s)). The Responsible Party may be either the initiator of the project or an entity selected by the Contributing Funder(s). The Responsible Party is responsible for the whole project and the other stakeholders contributes to the project through different manners such as provision of funds (The Contributing Funders), access and analysis of database/network or implementation of different aspects of the project (The Contributors).

The Scientific Committee should be composed of representatives from the Responsible Party, the Contributors, qualified scientists from the Contributing Funders and must include independent external experts.

The Audit Committee could be either a body exclusively constituted by independent experts coming from an organisation which is neither contributing in the decision making nor in the implementation/management functions, or a body with representatives from the Responsible Party, the Contributing Funder(s) and independent external experts. In that last case, representatives from the Responsible Party and the Contributing Funder(s) should be considered by their position and function as independent from those involved in the decision making process and technical and scientific advice.

In this type of collaboration, it is recommended to have a trustee to manage the financial assets especially in case of multiple funders. The decision to take a trustee and its selection should be discussed between the parties but may remain under the responsibility of the Responsible Party. In any way the Contributing Funder(s) should have no role in the allocation of funds to prevent undue influence in the implementation.


In general, transparent relationships between the Responsible Party and the Contributing Funder(s) are needed to avoid such undue influence which may affect the perception of the credibility of the results.

From a legal point of view, a Collaboration agreement must be signed between all parties involved, the Responsible Party, the Contributing funder(s), the Contributor(s) and the Trustee defining the roles and responsibilities of each party. Independent external experts participating in the Scientific Committee or the Audit Committee shall be part of the contractual agreement. The process for the selection of the Responsible Party by the Contributing Funder should be fully transparent and take into account the risks of potential conflicts of interest. Selection processes are presented in chapter 5.1.

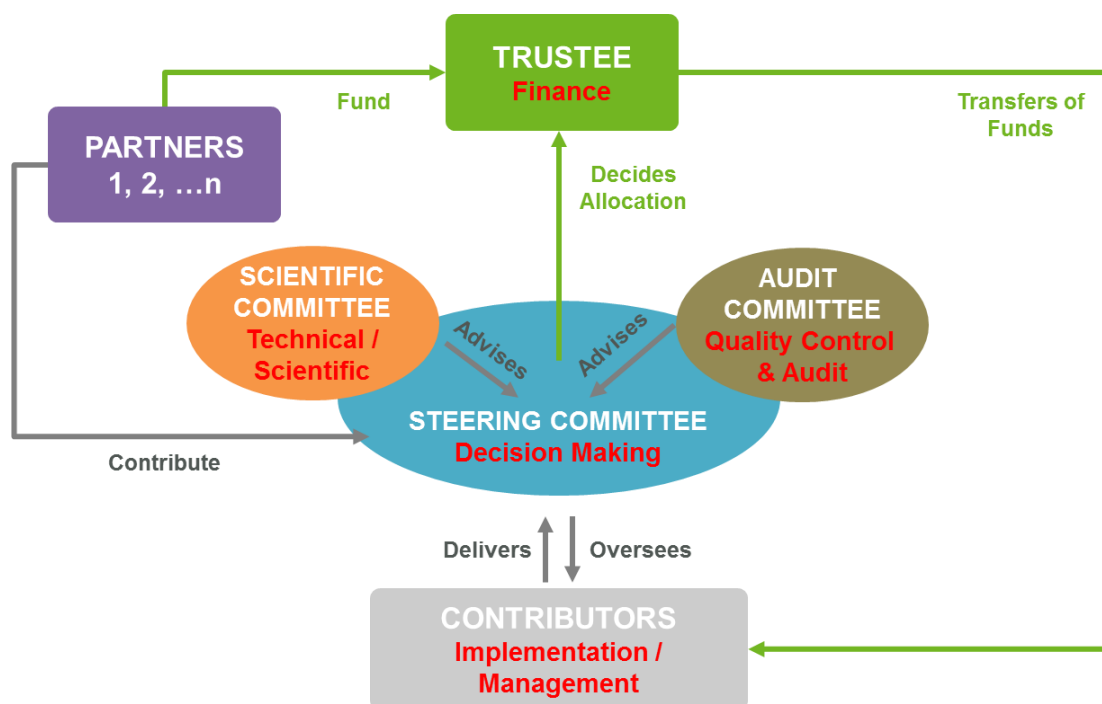
The legal and intellectual property related to the results should be discussed upfront between the parties and mutually agreed between the Responsible Party, the Contributing Funder(s) and the Contributors.

Co-authorship for publication should follow recognised international guidelines.

Some specific (pre-defined) use of results (such as submission to regulatory authorities as part of RMP) should be discussed upfront and agreed between the parties.

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Model 3: Partnership with shared responsibility and funding



The decision making function is shared between the partners and endorsed by the Steering Committee which is a governance body of partner's representatives. The Steering Committee should be composed of at least one candidate per partner who will represent its organisation. Partners of the Steering Committee are co-responsible for the overall joint project.


The Steering Committee may not be able to fulfil all the functions because of time, competencies or to reinforce the independency. The scientific and audit functions may be allocated to two additional committees which advise the Steering Committee.

The Scientific Committee should be composed of subject matter experts from the partners and must include independent external experts.

The Audit Committee could be either a body exclusively constituted by independent experts coming from an organisation which is neither contributing in the decision making nor in the implementation / management functions, or a body with representatives from the partners and independent external experts. In that last case, representatives from the partners should be considered by their position and function as independent from those involved in the decision making process and technical and scientific advice.

In this type of partnership, it is strongly recommended to have a trustee to manage the financial assets.

From a legal point of view, all the partners shall sign an agreement to set the terms and conditions of the partnership, with the roles and responsibilities of each party and governance body created for the

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conduct of the project, as for example, but not limited to, the Steering Committee, the Scientific Committee and the Audit Committee, with a clear and transparent description of the voting rules for the Steering Committee which is the decision making body.

The results generated by the project would be the joint property of all the partners. The agreement shall set all the terms and conditions regarding the intellectual property rights on those results to be discussed on a case by case basis. Some specific (pre-defined) use of results (such as submission to regulatory authorities as part of RMP or any other related documentation) should be discussed upfront and agreed between the parties.

Co-authorship for publication should follow recognized international guidelines.

4.3 Discussion

The table 1 below summaries the features and challenges of the three proposals for governance model with the level of acceptability by the stakeholders.



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Table 1: Characteristics of the governance models

	Model 1 collaboration self-funded by the Responsible Party	Model 2 collaboration with Contributing Funder(s)	Model 3 partnership with shared responsibility and funding
Characteristics	<ul style="list-style-type: none"> ✓ Dominance of the Responsible Party must be mitigated by a Scientific Committee (SC) with independent external experts. ✓ Easily implementable (from legal perspective) and manageable (communication perspective) model. 	<ul style="list-style-type: none"> ✓ More balanced membership of the Committees (composed of representatives from the Responsible Party, the Contributors, qualified persons from the Contributing Funder(s) and independent external experts) ✓ If the Contributing Funder initiates the project, the selection of the Responsible Party should be transparent and avoid potential conflicts of interest. ✓ Contributing Funder must have no role in the allocation of funds 	<ul style="list-style-type: none"> ✓ Model with expected high partners engagement and shared decision making ✓ Steering committee composition should be balanced between parties and voting process should be clearly defined and agreed upfront the project ✓ Most complex model to implement and manage due to the numbers of partners and complexity of decision making process
	<ul style="list-style-type: none"> ✓ The Scientific and Audit Committees must include independent external experts to ensure scientific and quality standard, ethic and governance compliance for transparent public-private interactions 		
Stakeholders acceptability	<ul style="list-style-type: none"> ➢ Could not be suitable for all public-private interactions (e.g. MAH/PHI) 	<ul style="list-style-type: none"> ➢ Preferred model for public authorities considering interactions with MAHs ➢ Reassured public partners confidence being public authorities making the decisions especially in case of very sensitive studies (e.g. safety studies) 	<ul style="list-style-type: none"> ➢ Preferred model for MAHs in case of regulatory commitment to fulfil legal obligations ➢ Reassured vaccine partners confidence being the spirit of mutually balanced collaborative project

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5. Developing a project Governance: practicalities

The aim of this chapter is to provide operational guidance and recommendations to help people building a suitable governance for a project.

5.1 How to build a project specific governance?

A. What is the vision and mission of the project?

The vision and mission of the project should be established including definition of the research question, the public health perspectives and the project constraints.

B. What is the need/added value and constraints to build a collaborative project?

The need and added value(s) of conducting the project through a public-private collaborative project should include both complementarity and synergistic roles between stakeholders. **Contribution could go far beyond providing funds, access to data or facilities.**


Successful collaborative projects begin with a clear understanding of why the partners are coming together, why their objectives cannot be achieved (or not as effectively) through any other means, and why the benefits will outweigh the costs.

C. What is the process for stakeholders identification & selection? What could be the most relevant governance model for the project?

The identification and selection of the stakeholders should be conducted in a transparent way and justified according to the project vision and mission. The number of stakeholders should reflect the needs of the project including expertise, resources, time and funds.

The reflection should start on what could be the most relevant governance model for the project, who could be the decision-maker and who could provide funds.

The "**Selection process guide**" section below describes and provides further recommendations on the criteria, processes and entities which should be considered in such step.

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Selection process guide

1. Introduction


In the models of collaboration (models 1 and 2 described above), the Responsible Party (RP) is the organisation or entity having responsibility and accountability for all aspects of the project. This includes making decisions on the strategic direction, design, conduct and reporting of the project and decisions on allocation of resources, taking into account recommendations made by appropriate governance bodies (e.g. Scientific Committee and Audit Committee).

Some projects are initiated and entirely funded by the RP itself (see Model 1 of governance models) who needs to collaborate with Contributors to conduct the project. Other projects are initiated by a public or private organisation that provides the funding (the Contributing Funder) but will not take on the decision making function (see Model 2 of the governance models). An example is the situation of a post-authorisation safety study that has been requested to a vaccine manufacturer by a regulatory authority. An issue in this model is the financial dependence that is established by a contract between the Contributing Funder (CF) and the RP. This dependence may influence (or be perceived to influence) the decision-making and affect the credibility of the RP and the confidence in the project results. As seen previously, the decision-making process needs to be fully transparent but this also applies to the selection process of the RP by the CF.

This section describes:

- Criteria that can be used for the RP selection;
- Processes for the selection of the RP by the CF, with their strengths and weaknesses;
- The role of eventual Selection Committee (SeC) and External Organisation (EO) who can be involved in some selection processes.

While they are applied to the selection of the Responsible party by the Contributing Funder (Model 2 of the governance models), the criteria and processes could also be used for the selection of other contributors in all governance models.

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2. Selection criteria


Irrespective of the selection procedure, a standard list of selection criteria should be used to select the candidate RP. These criteria relate to 1) their financial capacity, 2) their technical and professional capacity and 3) their ability to investigate a specific research question. Candidate RP must fulfil all of the criteria.

1) Financial capacity

- Evidence should be provided that the candidate RP is in a stable financial position and has the financial capacity to perform the project (irrespective of the funding received). The evidence may be based e.g. on a statement of overall turnover for the last two financial years, or a signed declaration regarding the financial situation. The documentation supplied should be reviewed to assess the general financial health of the candidate RP.

2) Technical and professional capacity

- Evidence that the candidate RP is authorised to perform the contract under national law with proof of authorisation provided by e.g. evidence of inclusion in a trade or professional register or a sworn declaration or certificate, or authorisation of entry in the VAT register.
- Evidence that the candidate RP has access to or is able to collect appropriate data and has experience in providing high quality service and expertise in the field relevant to the research question; this evidence should include a description of previous experience relevant to the field of project, including general processes in place to manage research projects and strategies to overcome difficulties and contingency planning. A list of relevant research (e.g. in the field of pharmacoepidemiology or vaccines) performed over the last few years should be provided, including links to relevant publications in peer-reviewed journals or project reports in the public domain.
- Evidence that the people involved in the project are sufficiently experienced and competent and free of related conflict of interest (CVs, publication lists and COI forms should be provided)
- Evidence that the candidate RP has in place clearly defined quality assurance methodologies and processes for conflicts of interest. The candidate RP should provide a short description of the general methodologies used for quality assurance in the research they undertake including measures for collecting, analysing and evaluating data. The description should also include reference to its processes to handle conflicts of interest.

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3) Quality of the proposal

- The candidate RP should describe an understanding of the project objectives, and a proposal for the overall project design, methodology to be applied, data source(s), data to be collected, outline of analysis, so that a correspondence between the proposal and the assignment requirements can be evaluated.

3. Selection processes

The choice of the selection process may be influenced by project characteristics in the field of B/R of vaccines such as the choice of countries where the project can be performed, the availability of relevant data, the specific expertise required for the project design and analysis, the potential impact on public health of project findings or the source of funding.

Three main selection procedures are presented: 1. Selection directly by the Contributing Funder, 2. Selection by a Selection Committee and 3. Selection by an External Organisation (Figure 1).


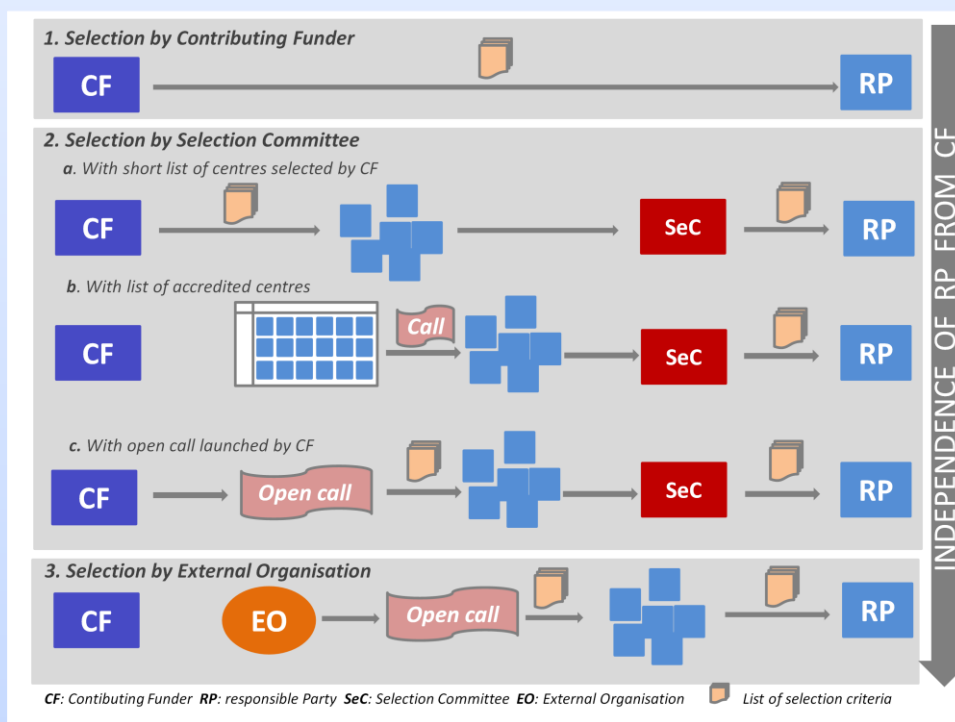
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Figure 1. Options of procedures for the selection of the Responsible Party (RP) by the Contributing Funder (CF).



3.1 Selection directly by the Contributing Funder

The Responsible Party (RP) is selected by the Contributing Funder (CF) based on the standard list of criteria. If several CFs are involved in the selection (for example in case of a joint project), the selection of the RP should be made according to rules agreed in advance (e.g. by consensus or simple majority).

- Strengths: speed
- Weaknesses: lack of transparency and lack of clarity on reasons for choosing a RP among other candidates; no systematic external verification of the compliance of the selection to the criteria; RP dependent on CF.
- Recommendation: this process is the least desirable one as the RP is not completely independent from the CF; however, it may be applicable if there is only one RP that can address the research question (access to a specific data source of national surveillance/vaccination program data); the selection process and the reason for choosing the RP should be documented and made publicly available.

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3.2 Selection by a Selection Committee

The selection process is managed by the CF with selection of the RP by a Selection Committee (SeC description made below in section 4.1). The CF follows the recommendation of the SeC or otherwise justifies any divergent opinion on the selected RP and this justification should be documented and made publicly available.

The selection of the RP by the SeC may be made through three different mechanisms.

a. Selection based on a short list of centres selected by the CF


The CF establishes a short list of possible RPs and submits this short list to the SeC. This short list can be established following a restricted call based on the research question.

- Strengths: speed; slightly decreased dependence of the selection procedure from the CF
- Weaknesses: unclear exhaustiveness of the short list.
- Recommendation: the short list of candidates should be established according to the standard selection criteria and the justification for their inclusion in the list documented.

b. Selection based on pre-existing list of accredited centres

The SeC selects the RP amongst expressions of interest received from research centres included in pre-defined list of accredited centres established through national or European systems. Expressions of interest for a specific project are solicited by the CF through a restricted call based on the research question and include a proposal for a project design to answer the research question. The pre-defined list of accredited centres could be based on a prior procedure initiated by a public institution, e.g. through an open call for expressions of interest to conduct observational vaccine studies, or through a national accreditation system. The list should be regularly updated. The list would also be available to other organisations such as the ECDC or EMA.

- Strengths: speed, provided that a pre-defined list of accredited research organisations has already been established; better guarantee that the research centre is competent and able to perform the project; higher independence as regards the CF.

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- Weaknesses: efficiency of the procedure depends on application of uniform accreditation criteria or establishment/existence of national or European accreditation system, and availability of a database of accredited research centres. Risk of conflict of interest with time given that these accredited research organisations become a pool of preferred partners and one can become too dependent of the resources generated by this mechanism (situation of monopoly). Specific questions (e.g. country specific) may not be answerable by a standard pool of accredited research organisations or may induce a lack of competition.
- Recommendations: this procedure may combine speed, rigor and independence; the list of accredited research organisations should be established prior to the research question and regularly maintained; it applies if the research question is not too specific.

c. Selection based on open call managed by CF


The SeC selects the RP amongst expressions of interest received from research centres that responded to an open call launched by the CF based on the research question and any other requirements.

- Strengths: large choice of candidate RP as all research centres may apply; selection procedure more independent from the CF.
- Weaknesses: slow procedure linked to time needed to launch the open call; uncertainty of whether all CF have the possibility to launch a public call.
- Recommendation: all steps of this procedure should be transparent.

3.3 Selection by an External Organisation

The management of the selection of the RP is delegated to an External Organisation (EO description made below in section 4.2). The EO selects the RP through an open call with selection by its own selection committee. The EO's selection committee assesses applications and selects the best candidate RP. The CF endorses the selection made by the EO.

- Strengths: large choice of candidate RP as all research centres may apply; selection procedure independent from the CF
- Weaknesses: slow procedure linked to the time needed to launch the open call; question on independence of selection of RP is cascaded to the selection of the EO.
- Recommendation: this procedure may be more relevant to study programmes that individual studies requiring quick results; this procedure would be most useful in case an EO has already been established (see below).

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4. Description of the Selection Committee and External Organisation

4.1. Selection Committee

The Selection Committee (SeC) is a committee chosen by the CF to select the RP based on the list of selection criteria. The SeC could be an ad-hoc committee composed of external independent experts nominated by the CF or an established committee from outside the CF (e.g. established by a public institution or a foundation). This last option is the preferred choice when such established committee exists and is relevant for the research project.

The justification for the choice of the selected RP should be made publicly available.

Criteria for the nomination of the SeC include the following:


- The SeC should have expertise in administrative, financial and scientific aspects of the selection procedure.
- The SeC should include at least three members; they should fill in Declarations of Interests that are made publicly available, notably the relationship they may have with the CF or potential RPs.
- The SeC may consult additional members with technical expertise on some aspects of the selection, for example on scientific aspects of the research question to be addressed.
- Members of the SeC should agree on the confidentiality of the documents assessed and of the discussions, except for the information made publicly available.
- Decisions of the SeC should be taken by consensus; in case of divergent opinions, the decision may be taken by simple majority and the divergent opinions should be made publicly available.
- Members of the SeC should be reimbursed by the CF for the time and expenses occurred based on published reimbursement rules.

4.2. External Organisation

The External Organisation (EO) is an organisation to which the selection of the RP has been entirely delegated by the CF. Criteria for the nomination of the EO for a specific study programme or single studies include the following.

- The EO is a research institution with large experience and expertise in management of research and a track record in selection procedures.
- The EO may be a research institution previously selected by a recognised national or international regulatory authority or public health institution, such as EMA or ECDC, through a suitable procedure.
- For a specific study, the EO may consult additional members with technical expertise on some aspects of the selection, for example on scientific aspects of the research question to be addressed.

- If appropriate, the EO may also serve as the trustee for a study programme or a specific study.
- The cost of the selection by the EO for a given study or study programme should be paid by the concerned CF(s) according to published reimbursement rules.

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D. How roles and responsibilities are distributed/shared?

The parties should finally agree on the most appropriate governance model and roles and responsibilities should be fine-tuned: distribution between stakeholders and creation of committee(s).

Specific terms of each party's contribution should be outlined in terms of resources, expertise and institutional capacity to help achieve the project' objectives.

The two sections below provide further description and recommendations on the relevance of body and organisation which are of interest for governance:

- **Role of the Trustee** and examples of such organisations
- **New role of Civil Society Organisations** and their relevance in vaccines project

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ROLE OF THE TRUSTEE


The function of the Trustee will vary depending upon the model of interaction employed. Fundamentally its role is to ensure independence of the financial processes from the decision making/implementation functions increasing confidence in the validity of the results. In addition, its presence provides a mechanism by which multiple stakeholders can contribute funds for a collaborative project but play no role in the allocation of the funds. The Trustee has no role in the scientific decision-making function.

Depending on the model the remit of the Trustee may include:

- To independently manage the financial aspects of the project, enabling transparent financial relationship between the contributing funders and the responsible party or the partners
- To hold and manage funds from multiple stakeholders centrally to ensure contributing funders have no earmarking of the funds
- To ensure that funds are spent appropriately by implementing appropriate monitoring processes.
- To provide appropriate records of financial accounts if required by the auditors and some public sector partners (separate account)

There are different examples of funding bodies who could potentially perform the Trustee function. Examples of such bodies include:

- CACEIS, one of the largest providers of fund depositary services in Europe, providing trustee services for a broad range of funds regulated by different legislations;
- the Bill and Melinda Gates Foundation, the Wellcome Trust, the Medical Research Council in the UK, all bodies with expertise in the area of vaccines and healthcare in Low to Middle Income Countries (LMICS) ; however these bodies also provide financial support and structures to facilitate the scientific decision making process and may prefer to ensure a wider function than the financial function outlined above (e.g. they may take the role of the External Organisation (EO) described in the selection processes).

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THE NEW ROLE OF CIVIL SOCIETY ORGANISATIONS

Civil society organisations (CSOs) are organizations and institutions that manifest interests and will of citizens. CSOs may be non-governmental organisations, advocacy organisations, professional and community associations (health care professionals, parents' federations, patients' groups etc.).

The prominent role of CSOs in global health initiatives came from the fight against HIV and AIDS and led in 2002 to the creation of the Global Fund. In the health environment, they are increasingly consulted by international organisations and, in some cases like the Global Fund, are involved in decision-making.


In the field of vaccines, some European and Women associations such as the European Cervical Cancer Association (ECCA) and the European Cancer Patient Coalition (ECPC) or national cancer leagues such as Jo's Trust in the UK have played an important role in the advocacy for HPV vaccination.

Promoting CSOs participation in collaborative vaccines projects is particularly relevant in the context of real life setting to monitor benefits and risks of vaccines and their vaccination programmes. **Working with experts, CSOs may be an important bridge from the science to the lay public.** This may provide a vital counterbalance to media hype and anti-vaccination groups. By being rooted in society, CSOs are in a better position to anticipate and address controversies around vaccination. **The active participation of civil society may allow to inform, to reassure and to contribute to improve the public confidence in vaccines and to reduce the perception of conflicts of interest.**

Civil society organisations may be involved in a wide range of activities and roles in the governance, including:

- members of the **Steering Committee** in public-private partnership; CSOs may be either considered as observer or with a voting right;
- members of **Scientific Committees** for health care professionals in public-private collaboration; bringing "real-life" experience in vaccination as well as specific knowledge and expertise in technical and scientific discussions;
- members of **Audit Committee** for persons with appropriate qualification and experience;
- **Independent external experts** consulting for the review of project information dedicated to external communication to lay public.

Efforts to actively include CSOs in public-private interactions is highly recommended as a guarantee of transparency and public interest; their role may also be important to decrease public perception of a lack of independency of public health institutes in collaborative projects with participation of vaccines manufacturers.

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E. How are the committees established?

Committees should be composed of representatives from collaborators/partners and independent external experts.

Committee members will have the following general responsibilities:

- Commit significant time to the project;
- Read documents, gain understanding of all issues,
- Participate fully in all committee meetings and discussions
- Share information with members
- Correspond with members on issues of relevance
- Establish strong working relationship with members

For Steering Committee, additional responsibilities will be:

- Seeking input from their organisation prior to committee deliberations (meetings, teleconferences,...) since they represent their organisation, or having a specific mandate for such project
- Reporting key issues back to the organisation after meetings, including the implications for the organisation.


COMMITTEES COMPOSITION

The size and therefore membership of a committee should be limited to ensure that the committee is able to operate efficiently. As such, non-members should not be able to attend meetings. But interested stakeholders that do not sit on a committee could, however, provide input to issues being discussed at the committee level. In collaborative project, stakeholders should be fairly and equitably represented on the committees.

Steering Committee: a balanced representation between the different public and private stakeholders should be considered; Relevant civil society organisation could have a seat with voting right to outweigh public and private sectors.

Scientific Committee: Representatives (qualified scientists) from collaborators or partners completed by independent external experts should be of interest. Independent external experts may be chosen based on their specific related expertise on the project field (disease, vaccine, ...) or to seek advice from broader fields (drugs, outside Europe,...).

Quality Control and Audit Committee: A majority of independent external experts could be in the interest of good governance and to ensure that the committee could draw upon appropriate expertise to fulfil its mandate.

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F. How are stakeholders' representatives nominated?

Each organisation should nominate members based on the Committee mandates, required competencies and responsibilities. The organisation should assign appropriately the person in regards with his/her **qualification, experience and position (documented in a CV)**. **One important factor is that nominated person should be able to provide the time required to contribute to the project activities.**

NOMINATIONS

For **decision making**, the nominated person should possess authority to represent, speak and vote on his/her organisation; he/she should be able to take decision engaging its organisation or enquire organisational approval through a quick and efficient way.


For **technical and scientific advice**, the nominated person should have scientific skills relevant for the project. In addition, for commercial organisations (such as MAHs) this function must be assigned solely by personal from Medical and Scientific departments; marketing department personnel and sales representatives cannot be eligible for this function. The nominated members of this group are not supposed to represent their organisation but they are supposed to contribute based on their individual expertise.

For **quality control and audit**, the assigned person should furthermore be considered independent of the decision making process and the implementation and conduction of the project.

G. What is the need for external expertise and how external experts are selected?

It is highly recommended to involve external experts to take part in the project in the Scientific Committee and in the Audit Committee. The process used to select external experts should be done in a transparent way and justified according to the project vision and mission. It should be a skills-based process, with qualification and experience documented in a CV. External experts' role should be described in the agreement. Potential COI of external experts should be duly documented and considered.

Experts' compensation should be justified through dedicated tasks/services, estimated workload and on line with country fair market value.

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5.2 How to set up a collaborative agreement?

H. What are the legal considerations in collaborative projects?

- Collaboration and partnership by definition must lead to mutually satisfactory outcomes; each stakeholder must have a real role as contributor in the project, which includes also legal rights granted to each of them depending on the project and the level of the contribution. The basic principle of efficient collaboration and partnership is to agree, from the beginning of the reflection, the sharing with the collaborator/partner(s) of some of one's own asset, data, knowledge or expertise and to agree to grant some relevant rights on these; the negotiation shall be done in good faith and freely between the parties except within the limits of what they cannot deviate from certain mandatory rules and regulations. In case of conflicts between parties, the ADVANCE Code of Conduct must prevail.
- To implement a sustainable and transparent collaboration or partnership the payment of any funds shall be done to a legal entity (an institution, organisation) and not to an individual to avoid any fraud or misperception except in case of independent external experts; the amount of any funds must be clearly estimated according to real needs and represent a fair market value of the needs, negotiated in an arm's-length transaction.
- The right to privacy is a highly developed area of law in Europe, the Data Protection European Directive (officially Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data), adopted in 1995, regulates the processing of personal data within the European Union. It is an important component of EU privacy and human rights law. Personal data should not be processed at all, except when certain conditions are met. These conditions fall into three categories: transparency, legitimate purpose, and proportionality. Consequently the transfer of personal data is strictly regulated and collaborator or partner cannot request more than what is allowed by the law, personal data are protected and the potential user or entity which could have access to those personal data are controlled and audited;
- Publication rights should be discussed before the project start and shall be described in the agreement keeping in mind that any publication shall be made in accordance with the professional standards as internationally admitted for the publication of scientific results and authorships; collaborators or partners cannot deviate from these rules in any way.

I. What should be documented in the agreement?

- In the core document:
 - The preamble with the objective of the research project, a description of the Parties and the rationale for the collaboration/partnership
 - The Project work plan and period with key tasks and associated timelines
 - The rights, obligations and contributions of each Party
 - The composition, obligations and contributions of the different committees
 - The decision making process
 - The subcontracting activities when applicable
 - The records and project deliverables
 - The compliance with regulations: ethics, data privacy and pharmacovigilance.
 - The financial conditions: budget, funding source, schedule and terms of payment, transparency and financial disclosure
 - The confidentiality

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- The publication plan
 - The Intellectual property and data ownership
 - The Insurance
 - The warranties with conflicts of interest
 - The term and termination of the agreement
 - The applicable law and competent Court
- In appendix:
- Full description of the project and related tasks allocation
 - Brief description and/or CV of the persons involved in the project: stakeholders representatives and external independent experts
 - Organisational and personal declarations of Conflict of Interest
 - Detailed budget and planned resources allocation
 - Protocol if applicable

The ADVANCE working group is developing **contract templates** (one per governance model) which will be proposed as a **support for a rapid implementation** of future public-private collaborations/partnerships in line with the recommendations of the ADVANCE Code of Conduct. It is hoped that these contract templates can provide agreed and acceptable formats to establish public-private interactions for future projects and therefore will not have to be entirely developed and only adapted for each project.


DECISION MAKING RULES

In the beginning of the process, stakeholders need to agree what kind of decision-making process will be used. The priority should be made on achieving the objectives of the project rather than seeking compromise between the interests of different stakeholders.

Consensus is the preferred method of decision-making because it will generate better solutions and commitment by all. Seeking consensus will urge stakeholders to find an agreement that incorporates all points of view. The appropriate time of voting should also be agreed.

Our recommendation is to strive for consensus but introduce a majority vote to bring about a conclusion and make the decision, if necessary. The decision can be reached when the respective majorities of the stakeholders represented are in favour of it. Minority viewpoints should be recorded in final decisions when consensus cannot be achieved.

Entering into decision-making should not happen too early, waiting for the dialogue process and the development of all new ideas; but also not too late endangering public health and trust.

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An escalation process should be planned where a decision cannot be reached or major issues, concern or objection is raised. The escalation could consider seeking external advice from experts or from specific organisations/institutions/authorities.

Voting level option could be the following: decision process requires a quorum of 2/3rd of the members to be present in order for a vote to be taken. 75% qualified majority vote decision will apply.

The procedures and methods of decision-making should be open and transparent so that effective participation is possible. Agenda's, presentations and meeting minutes should be recorded and accessible to all stakeholders.


Decision making in collaboration: The Responsible Party, is the decision maker; voting rights could be applied when the decision making process is handled by different persons within the organisation.

Decision making in partnership: The steering committee with representatives from several stakeholders is the decision maker; committee composition and voting rights are of interest especially for shared decision making in public-private partnership.

All opinions/recommendations made by Committees (Scientific and Quality Control & Audit) need to be clearly documented and the decision maker should consider all the recommendations made. Any deviation from its recommendations in the final decision making should be duly recorded and justified to ensure transparency.

J. How to assess, manage or mitigate Conflict of Interest?

Both organisations and people should declare their interests at the beginning of the project. Declaration of Interest forms should document actual or potential conflicts of interest.

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CONFLICT OF INTEREST


Ensuring that the integrity of decision-making in vaccines B/R project is not compromised by organisational and personal conflict of interests is a growing public concern. Interactions between public institutions, public authorities and marketing authorisations holders (having commercial interests) present new challenges. In case where it has been decided that a private contribution is necessary or useful, conflict of interest situations cannot be avoided by simply prohibiting a private company's participation in the project; in such cases, both the public and private stakeholders must take the responsibility to identify and mitigate problematic situations, setting compliance standards and establishing effective management. Training may be necessary to ensure that all stakeholders actually understand the conflict of interest ins and outs.

Conflicts of interest are both a straightforward and a complex matter: in principle, it is easy to define but in practice mitigating conflicts of interest can be a complex task. This requires technical skills and an understanding of many issues which are usually involved.

It is highly recommended to involve both stakeholders' compliance representatives and external compliance experts in the discussions about conflict of interest. In practice, we suggest to step up the Quality Control and Audit Committee at the earlier stage to assess, manage and mitigate conflict of interest.

The following stepwise approach may be of interest in collaborative public-private projects:

- Document organisational and personal interests and identify their related risks for the project; Conflicts of interest should not be limited to financial and commercial activities and should acknowledge academic competition, scientific publication and/or beliefs as well as personal and/or familial relationships; This is also important to distinguish between "actual", "apparent", "real", and "potential" conflict situations.
- Share stakeholders' own conflict of interest policy; engaging stakeholders representatives to review the conflict of interest policy of the different parties may be a good approach to have their views on the applications and problems for the project.
- Ensure that proposed standards of conflict of interest policies reflect mutual expectations for the project; consultations could be used to identify or negotiate mutual acceptable solution when relevant.
- Anticipate potential conflict of interest situations in regards with the project objective, raise awareness among stakeholders and include safeguards against potential conflict of interest.
- Review together high-risk situations and set up mechanisms that could minimise conflict of interest; ensure that relevant interests are to be disclosed transparently, ensure that decision-making procedures at all stages can be audited for integrity and justified.

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K. How is communication handled?

A plan should be established to detail the communication flow between the organisations / committees / members, the timing and frequency of the face to face meetings, teleconferences and information emails. Standing agenda and meeting minutes should be used to prepare and report objectives, discussions, decisions taken and address escalation. The communication plan should be agreed by the stakeholders before the project starts.

Project related documentation should be accessible at any time by all stakeholders.

COMMUNICATION AND TRANSPARENCY

Public-private interactions require transparent communication channels. People need to be able to know who is talking to whom, when and about what. On the other hand, decentralised, flexible, and spontaneous communication is suitable to build trust and discover commonalities. There is a need to strike a balance between those benefits and the need for transparency.

In the same vein, public-private interactions need to be as transparent as possible towards the outside. Decisions need to be taken regarding what information should be available to the general public. **In the context of vaccine B/R monitoring, collaborators or partners should face the challenge and aim to make the public-private governance and the project results understandable to the public.** A good strategy may be to identify at the early stage target audiences (Scientific congress, specific working groups...) and develop relation with key information sources (official websites for wide public communication and consultation such as European or national institutions or authorities and civil society organisations...).


6. CONCLUSION

This report presents the view of the ADVANCE working group on the governance principles and proposed models for public-private collaborative project in vaccines B/R monitoring. Governance triggers and challenges have been integrated to maximise the added value of interaction and mitigate stakeholders constraints, ensure transparency in the decision making process, identify and manage the conflicts of interest and ensure scientific relevance, ethic and compliance for the public health benefit.

Because public-private governance is a challenging topic in the field of vaccines, with various opinions among stakeholders across Europe, the ADVANCE working group has decided to solicit inputs from a larger group of stakeholders before finalising this governance guiding report in 2017. A workshop will be held at EMA office in London on 23 and 24 March 2017.

The workshop will have a double objective:

- Present the ADVANCE governance guidance to ensure that both the Governance basics for public-private interactions and the ADVANCE proposals (principles, models and processes for implementation) are well understood

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- Identify critical success factors supporting its adoption, main obstacles needed further adaptations and plans for its implementation by all stakeholders

The expected outcomes of this workshop will be to clarify the Governance concepts, evaluate the acceptability of the ADVANCE proposals, assess the need to modify/add to the proposed Governance models, and agree on plan of actions for guidance implementation. These outcomes will be integrated in the final version of this Governance guidance in 2017. The workshop represents a key validation step to insure Guidance relevance, acceptability and usefulness for a successful implementation of public-private collaborative projects in real live.

It is hoped that then governance standards developed by the ADVANCE working group will become the norm for future vaccines B/R collaborative projects for a rapid implementation and efficient execution.