Public-private collaborations and partnerships for vaccine benefit-risk monitoring in Europe: the ADVANCE framework and governance principles

Report of a workshop organised by ADVANCE [1]

European Medicines Agency - London UK - March 23th & 24th 2017

Workshop organisers and authors: ***Laurence Torcel-Pagnon (Sanofi Pasteur, France), Xavier Kurz (European Medicines Agency, United Kingdom), Vincent Bauchau (GlaxoSmithKline, Belgium), Cédric Mahé (Sanofi Pasteur, France), Myint Tin Tin Htar (Pfizer, France), Anne Charrat (Sanofi Pasteur, France), Angus Thomson (Sanofi Pasteur, France), Rafal Swierzewski (European Cancer Patient Coalition, Belgium), Patrick Mahy (Scientific Institute of Public Health, Belgium), Marianne van der Sande (National Institute for Public Health and the Environment, The Netherlands), Tyra Grove Krause (Statens Serum Institut, Denmark) and François Simondon (Research Institute for Development, France).***[2]

This document was prepared with editorial assistance from ***Margaret Haugh, medical writer, MediCom Consult, France.***

Final version

Dissemination level: ADVANCE website (http://www.advance-vaccines.eu/)

[1] ADVANCE project see: **http://www.advance-vaccines.eu/**

[2] Disclaimer: the opinions summarised in this report are those of the workshop participants and do not necessarily reflect the opinion of the organisations they represent. All workshop participants had the opportunity to see the report before publication

1. Summary

One key ambition of ADVANCE is to create a platform that facilitates open and fruitful discussions between key public and private vaccines players for the development of a collaborative approach for the monitoring of vaccine benefits-risks (B/R) in Europe. Working together in a collaborative approach is one way that could maximise resources and public confidence in vaccination thereby increasing the impact on public health in a challenging context for various situations in Europe.

About 70 senior experts attended the workshop organised at the European Medicines Agencies offices in London. It successfully allowed open discussion from a large panel of European experts in vaccine B/R monitoring on the challenges to be faced when setting up public and private interactions, using a concrete proposal of a governance framework put forward by the ADVANCE group.

The workshop attendees confirmed the need to establish a clear and transparent governance framework that is understandable and accepted by the scientific vaccine community and applicable to the European context for vaccine B/R monitoring. However the attendees emphasised that the level of acceptability of such sensitive interaction and the acceptance of the proposed governance models was not the same for all stakeholders[3] and for the various countries. In reaction to discussions during the workshop, ADVANCE will adapt its governance framework, to provide key principles and a generic model with options to enable adjustments to take into consideration the context and the project specificities. This adapted ADVANCE framework should facilitate the implementation of future public-private projects and should be seen to contribute added-value to the promotion of this collaborative approach of working.

[3] A stakeholder is an individual, group or organisation that is impacted by a process or decision, and that may or may not be actively involved in the process or decision

2. Background

The 2009 influenza pandemic highlighted the various challenges key stakeholders[4] in the vaccine field had to face, and how these limited their individual capacity to collect European data on pandemic vaccine exposure, safety and effectiveness rapidly to be used to make informed decisions on the benefit-risk. One way of overcoming these challenges is the creation of collaborations and partnerships that leverage the assets of the public and private sectors collectively. This underpinned the creation of the collaborative project: ADVANCE[5].

ADVANCE (http://www.advance-vaccines.eu/) is an on-going 5-year Innovative Medicines Initiative (IMI; http://www.imi.europa.eu/) project (October 2013 - October 2018) established to develop a framework for public-private interactions that could rapidly provide robust data on post-marketing vaccine B/R monitoring to support decision-making in Europe. ADVANCE is a unique forum for the development of this framework for public-private interactions because of the range and number of public and private stakeholders in the consortium. In addition to the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA), there are 11 public health institutes (PHIs), 10 national regulatory authorities, 9 academic institutions, 2 clinical research organisations (CROs) and small and medium-sized enterprises (SMEs) and 7 vaccine marketing authorisation holders (MAHs).

One of the objectives of ADVANCE is to develop governance guidance to support the development of public-private interactions for vaccine B/R monitoring projects and facilitate a rapid implementation of these collaborative projects, when required, in Europe after the ADVANCE project. A working group within ADVANCE drafted a framework that proposed governance principles and processes to support the development of efficient, transparent, ethical and trustable public-private interactions in Europe. However, it is a controversial topic, with diverse opinions among stakeholders across Europe. Therefore, the IMI recommended that ADVANCE should organise a workshop to solicit input from a larger group of European stakeholders (public health institutes, health organisations, patients associations and other organisations that are not part of the ADVANCE consortium).

This report summarises the content of the workshop and outlines how the input will be used to finalise the governance framework.

[4] A stakeholder is an individual, group or organisation that is impacted by a process or decision, and that may or may not be actively involved in the process or decision

[5] ADVANCE is a 10M€ project, with 5M€ from the EC to finance the contribution of the public sectors and 5M€ from vaccine market authorisation holders through in-kind contributions to the project

3. Objectives

The aim of this workshop was to address the question: how can we most efficiently and equitably set up public-private collaboration or partnership for vaccine benefit-risk monitoring in Europe and work together in full transparency?

The workshop was based on the assumption that some attendees intended to enter into a collaborative public-private project, with shared common goals and interests. The main objectives of this workshop were to:

- ensure a common understanding of the proposed ADVANCE governance concepts, framework and proposals for collaborative public-private interactions
- discuss how best to organise the governance of these multi-stakeholder interactions, while making them acceptable to participants and taking into consideration their experience, willingness and capacity for implementing the proposals outside the ADVANCE consortium
- identify critical success factors, main potential obstacles and solutions that may need to be developed and assessed to overcome these obstacles.

4. Organisation of the workshop and participants

About 70 senior experts involved in vaccine benefit-risk monitoring in Europe and/or the development of public-private interactions were invited to the workshop. Among these participants, more than 50% represented organisations that were not members of the ADVANCE consortium. There were 14 participants from national public health institutes and ECDC, 8 from national regulatory authorities and EMA, 20 from academic institutions and CRO-SME, 16 from MAHs, 8 from patients' associations and health organisations. Several European, countries were represented such as UK, Belgium, France, the Netherlands, Germany, Italy, Denmark, Sweden, Switzerland, Finland, Ireland, Norway, Poland, and Spain.

An invitation to participate in a pre-workshop on-line survey was sent to all participants to collect information about their experience with public-private collaborations (PPCs) or partnerships (PPPs). A total of 44 participants responded to at least one survey question. Most of the respondents were from public health institutes followed by MAHs. About 70% of the responders had been or were still involved in a PPC or a PPP. Among the 14 who had not been involved in a PPC/PPP, 9 said they had not had a pertinent opportunity and the remaining 5 said it was because of legal reasons, institutional policy, need for ministry of health approval, potential conflicts of interest or the need to be seen as being independent. The main objectives of the PPC/PPP they were involved in were vaccine effectiveness/impact, vaccine safety, vaccine development, drugs and others. The main reasons given for participation were for the science, evidence-based data, sharing, public health, and having a specific role in the PPP/PPC. All the responders of the finalised PPCs/PPPs said that the objectives had been attained; 13% said the projects were still ongoing.

They said the added-value for participating in PPCs/PPPs included the better use of resources, for the common good, networking, collaboration for excellence, building trust and transparency. The obstacles or barriers were the potential conflicts of interest, the perceived lack of independence, ownership of the data and bureaucracy. The respondents said the critical factors for success were clear governance models, consensus, transparency, scientific integrity and mutually-shared goals.

Their expectations of the workshop included understanding the strategy of ADVANCE, understanding the principles of PPC/PPPs and how to overcome hurdles, learning from others' experiences, understanding other stakeholders' perspectives and going beyond the usual objections.

The workshop, which was organised around plenary sessions and breakout sessions, was chaired by Hans-Georg Eichler (EMA). It was intended to be interactive with active participation from the participants, based on their personal expertise, experience or interest in public-private collaborative projects. The full programme can be found in Appendix 1.

The plenary sessions on the first day were dedicated to presenting the ADVANCE project with stakeholders perspectives and the governance proposals (Vincent Bauchau (GSK), Marianne van der Sande (RIVM), Xavier Kurz (EMA) and Laurence Pagnon (Sanofi Pasteur)), Then the participants were divided into four stakeholders groups (Group 1: public health institutes, Group 2: regulatory authorities/patient associations/health organisations, Group 3:

academic institutes/CROs/SMEs and Group 4: vaccine MAHs) and a group of 8 legal experts from different organisations for breakout sessions in separate rooms. The stakeholder groups were asked to identify the critical success factors, main obstacles and solutions that should be investigated for the implementation of the ADVANCE governance proposals from their stakeholder point of view. To guide their discussions, they were asked to answer five questions and to summarise their discussions to be presented in the plenary session afterwards by a rapporteur. See Appendix 2 for the list of group participants and questions. The legal expert group were asked to discuss what legal barriers to setting up PPCs/PPPs could be expected and what potential solutions could overcome them. The group also received five questions to guide their discussions and were asked to summarise their discussions in a presentation to a plenary session afterwards by a rapporteur (Appendix 2).

The second day, the plenary sessions explored aspects of public trust in PPCs/PPPs for vaccine benefit-risk monitoring projects. After that, the participants were allocated to a breakout session involving representatives from different stakeholders to discuss how to develop pragmatic approaches to ensure public confidence in private-public collaborative projects (Appendix 3). Once again, the groups were provided with five questions to help guide their discussion and were asked to summarise these discussion in a presentation to a plenary session afterwards by a rapporteur.

5. What was presented

Day 1: ADVANCE governance proposals

Xavier Kurz (European Medicines Agency) and Laurence Pagnon (Sanofi Pasteur) presented the generic framework used to develop project-specific governance in vaccines B/R monitoring projects. Governance models already exist for big structures or long-term projects such as The Global Fund, GAVI, IMI, but there are for studies/projects generally only informal governance structures established on a case-by-case basis. ADVANCE recognises the effective added-value that transparent governance guidance could provide for the engagement of public and private stakeholders at the European level.[6] The capacity for collecting vaccine coverage, safety and effectiveness data in Europe is restricted because many data sources are not easily accessible and interactions between the multiple stakeholders (i.e., regulatory authorities, public health agencies, academia, and vaccine market authorisation holders) are not easy, partly due to perceived conflicts of interest and to a certain extent, funding issues. However, the success of some European consortia in vaccine effectiveness (I-MOVE) and safety (VAESCO) demonstrate that multinational collaboration is possible. Creating collaborations and partnerships that leverage the assets of the public and private sectors collectively could be a powerful means to ensure impact, scale and sustainability for the public health benefit and confidence in vaccines. The key stakeholders' contributions to vaccine B/R monitoring were presented. The mutual benefit of interactions between public health institutes, academic institutes, CROs-SMEs and MAHs could include complementarity of expertise, collective intelligence, multi-sectorial approach with higher impact, harmonised communication on vaccine benefit-risk monitoring and synergy in resource allocation and data access.

The framework and guidance developed by the ADVANCE group is based on key principles; that include engaging stakeholders collaboratively, ensuring transparent decision-making processes, identifying and managing institutional and individual conflicts of interest (CoIs) and guaranteeing scientific integrity, relevance, ethic and compliance for the benefit of public health while keep the solution as simple as possible. They are developing tools and processes for the implementation of these principles.

The governance is articulated around five key functions with clear and predefined roles and responsibilities: decision making; technical and scientific advice; quality control and audit; implementation and management; and finance (see appendix 4).For the sake of clarity, PPCs and PPPs were defined as follows:

- PPC: **only one partner is the decision maker** (and is also legally responsible and accountable for the project) with committees established to share advisory roles, involving partners and with external experts (scientific advisory committee, audit committee).
- PPP: **a governance body** (steering committee) **is created to establish shared-decision-making with representatives from the different partners.**

[6] 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(15):1844-55.

An ADVANCE Governance working group was established to work jointly on guidance for the governance for public-private collaborative projects for vaccine B/R monitoring. 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. The definitions, functions and bodies in the governance structure were adapted to fit with ADVANCE scope. Scenarios frequently encountered by the working group members (taking into account different real life research questions and contexts) were used to discuss and describe the added value and challenges of PPCs/PPPs and to clarify functions, roles and responsibilities of the different stakeholders and prerequisites for governance bodies. Draft governance guidance was 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. 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 this 2-day workshop in March 2017 during which two proposals for governance models were presented and discussed (Figure).

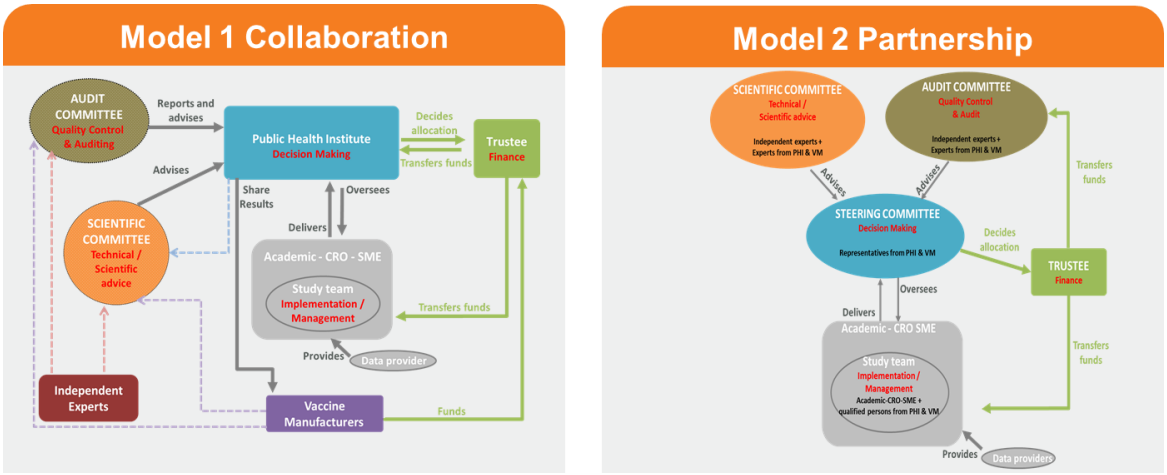

Figure: Schematic representations of governance models for public-private collaboration and public-private partnership involving PHIs and vaccine MAHs

The challenges facing ADVANCE include ensuring that the proposed models are acceptable for stakeholders and that a consensus can be reached on the models with the aim of developing guidance and tools that will contribute to a more rapid implementation of future collaborative projects for the assessment of vaccine B/R.

Cédric Mahé (Sanofi Pasteur) stated that many PHIs say that national or institutional legal considerations may be potential barriers to public-private interactions, or could make them complicated, in some countries. As an example, he took the situation in France to investigate these potential barriers. The French law no. 2011-2012 of 29 December 2011 on the strengthening of the drugs and health products includes an article on the need to declare

conflicts of interest and another allowing the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM: the French FDA) to issue calls for public health studies (pharmacovigilance/epidemiology) provided that they are not funded by one or more pharmaceutical companies. This law does not say that the French PHI cannot participate in PPPs/PPCs, but it is important to have a transparent governance model so that the funder is not involved in collecting and analysing the data.

Two examples of real-life governance models

Tin Tin Htar Myint (Pfizer) and Patrick Mahy (WIV-ISP) presented real-life examples of a PPC and PPP, respectively, which were set-up before ADVANCE. In the example of a PPC that evaluated the effectiveness of a vaccination programme in a real-world setting, the MAH provided funding and established a contract with an academic institute who was responsible for decision making. A scientific committee comprising representatives from the MAH, academic institute and PHI provided technical and scientific advice. Data were provided by the PHI, funded by the academic institute. The study team was composed of members of the PHI and academia. An audit committee was responsible for quality control and could perform audits, if requested by the MAH. The example of a PPP was a study that compared different diagnostic tools for breast cancer. The study was funded by all the MAHs who manufactured the diagnostic tools being compared. The steering committee, which comprised representatives from the MAHs, the PHI and independent experts, was responsible for decision-making and the allocation and transfer of funds. A scientific committee with a similar composition approved the study protocol, results, publications and other communication. The PHI provided the study team responsible for implementing and managing the study. The PHI subcontracted the quality control and audit to independent experts (audit committee). These examples show that ADVANCE's proposed governance models could be adapted to meet the needs and constraints in real-world settings. However, it was shown that setting up these projects on a case-by-case basis was time-consuming. Having governance models that can be adapted would reduce the time and efforts required as the process is formalised.

Day 2

Public perception of health collaborations/partnerships:

Although public perception of PPCs/PPPs for vaccine B/R studies was not an initial objective of the ADVANCE project it has been included following the discussions that the ADVANCE partners had about governance, when the importance of building and maintaining public trust became obvious. Angus Thomson (Sanofi Pasteur) gave the WHO definition of 'partnership' which is the bringing together of a set of actors 'for the common goal of improving the health of populations based on mutually agreed roles and principles'. He went on to present results from an unpublished survey to assess public trust that was conducted in the US, UK, Mexico and France.[7] These results showed that participants from the UK and Mexico trusted vaccines, medications, and PHIs significantly more than those from the US and those from

[7] Thomson et al, unpublished results

France trusted significantly less. Participants from Mexico trusted pharmaceutical manufacturers significantly more than those from the UK and the US; those from France trusted them significantly less.

All actors generally have multiple CoIs, which are not only financial. The WHO says they are often faced with a combination of converging and conflicting interests when developing partnerships with non-State actors. He cited a quote from Wynia (2007)[8]: "success in public health relies on public trust". Trust has been shown to be a multidimensional entity composed of integrity, reliability, openness, competence and benevolence. A comparison of global public trust in government institutions, businesses, media and NGOs surveyed in 28 countries in 2016 and 2017, showed a 3% decrease in global trust, the level of trust decreased in 21 countries and that 2/3rd of the countries were distrustful of these structures.[9] This highlights that public distrust of MAHs is not so different from public distrust of governments.

Trust between the partners in a PPC/PPP was shown to have a positive effect on innovative outcomes, and on the overall performance of the partnership.[10] One key success factor has been reported to be consistent, early and frequent communication. A transparent process, based on open communication, information sharing, shared decision-making process can increase the level of trust in PPPs, particularly from non-participating stakeholders.[11]

Understanding collaborative projects and determinants for public trust

Rafal Swierzewski (European Cancer Patient Coalition, Belgium) said that understanding the determinants of public trust in general can help us understand how to foster and maintain public trust in healthcare. A postal survey study that assessed if the public trust was in the healthcare system or the healthcare professionals in the UK showed that the respondents expressed much more confidence and trust in healthcare professionals than in healthcare managers. He said we cannot provide a dry administrative description about a PPP to the public; we have to communicate in a way that will allow the public to identify and thereby understand the objective of the collaboration. The public need to understand, the methods, who is responsible for what, what the expected outcomes are, the cost and who will benefit.

The governance models that have been used for some healthcare NGOs are similar to the proposed ADVANCE PPC model, but with different names for the various entities. These NGOs have been shown to work and are generally trusted by the public. Therefore, to develop public trust in PPCs/PPPs, we should have public input, a clear target group, be transparent and use ethical methods, as in the NGO model. Sharing information builds relationships between the general public and the PPC/PPP. The general public needs to understand and be understood,

[8] Wynia MK. Public health, public trust and lobbying. Am J Bioeth. 2007;7(6):4-7
[9] 2017 Edelman Trust Barometer available at http://www.edelman.com/trust2017
[10] Wong EL, et al. How shall we examine and learn about public-private partnerships (PPPs) in the health sector? Realist evaluation of PPPs in Hong Kong. Soc Sci Med. 2015;147:261-9
[11] Grotenburg et al. The influence of trust on innovative outcomes in public-private partnerships. Paper from 18th Annual Conference of the International Research Society for Public Management (IRSPM)
2. Corrigan, MB, et al. Ten principles for successful public/private partnerships. Washington D.C. Urban Land Institute, 2005

and their doubts, which do not mean distrust, need to be addressed, particularly the doubts of those in the target group. The general public will trust the decision-making and risk minimisation processes in benefit-risk studies, if they can draw similarities with what they experience in the daily life. And finally, long-lasting, stable results from a sustainable PPC/PPP will contribute to increase public trust.

6. Discussion points

This workshop facilitated open and lively discussions and an exchange of ideas and concerns about how public and private stakeholders could interact in collaborative vaccine B/R monitoring projects and take part in the development of a future sustainable framework. However, one of the key lessons learnt is that PPC/PPs risks and stakeholders constraints were more largely discussed than benefits and added-value of working together. It should be acknowledged that building trust in the vaccines stakeholder community may take time and thus emphasising the value of 'quick wins' in on-going collaborative projects.

Stakeholders visions and perspectives

Stakeholders have different concerns about the various missions and expected outcomes for a given project, e.g., exploratory analyses; rapid results; regulatory commitment, compliance with guidelines (good pharmacovigilance practices (GVP)); quality control of data; publications; timelines.

The PHIs said their mandate is to ensure continuous effectiveness and safety evaluations of the vaccination programmes at the population level. They can also run their own safety assessment studies, sometimes in response to a crisis when they need to use data that have not been fully quality-controlled to provide rapid answers before further in-depth investigations are performed.

MAHs said they are responsible per legislation for assessing and monitoring the B/R profile of their vaccines. MAHs have very strict standard operating procedures (SOPs) and need to act on 'SOP-quality' data. MAHs also said they were concerned about results being interpreted, without taking into consideration their inputs; the various stakeholders recognise the scientific expertise of MAHs in vaccines acquired during the clinical development of their products. They expressed concern about results being interpreted by a single stakeholder's point-of-view, if studies are conducted by only one organisation.

Regulatory authorities said they should not be involved in PPCs/PPPs aiming to answer product-specific regulatory questions to avoid influencing the interpretation of the results, but they could provide their formal scientific advice via the existing consultation processes.

The academic institutions said one of their main objectives is the publication of results, and therefore in these types of projects they would be unable to accept any constraints concerning the dissemination of results, once they are available.

PHIs said that having PPCs/PPPs in place could strengthen the preparedness in the event of an emergency vaccination issue only if this enables vaccine B/R assessments to be more rapidly implemented or modified, when required, and allow the rapid dissemination of preliminary results. Additionally, any early alerts from vaccine B/R assessments performed elsewhere could be shared rapidly.

PHIs said that the various PHIs in Europe have different political, legal and financial contexts and they do not have the same historical experiences. This can result in different perceptions of the benefits and risks of PPPs/PPCs. The public health priorities are not

necessarily the same in different countries and therefore the vaccination programmes differ in terms of which vaccines are included in the national recommendations and also which populations are targeted. This will have an impact on which specific studies/projects they would want to collaborate in.

One of the major challenge for PPP/PPC governance in this setting is the need to take into consideration the differences between the stakeholders and build on their strengths in order to maximise the potential benefits from the PPPs/PPCs.

Trust, scientific independence and communication

The importance of distinguishing two levels of trust was highlighted. The first level is between the stakeholders in the PPC/PPP and the second between the PPC/PPP and the public. Trust is earned by showing continuing trustworthiness, which takes time to develop.

The PHIs said that there could be a risk for the loss of scientific trust if they were to participate in PPCs/PPPs, due to perceived or real COIs that could damage their reputation. They said that strong safeguards would be needed to protect their scientific independence. For them, the independence of the scientific committee, which is essential, could be guaranteed, if the requirements for membership are clearly defined, in terms of the expertise, experience and transparency for COIs. They said that they need to trust the results, and to understand differences in their interpretation. It is important for them to be able to communicate well about how the results have been interpreted.

The MAHs said they need to build trust in the scientific value of their knowledge and expertise in vaccines. It is essential for them to ensure that all collaborators/partners are compliant with GVP, which requires, in particular, a high level of traceability and quality of the study data. They suggested that the inclusion of independent experts, i.e. from organisations not involved in PPCs/PPPs, could improve trust in the results and their interpretation.

The RAs said that it is important to maintain public trust, irrespective of who provides the data, with their evaluation of the study results being a key factor. To maintain this public trust, they cannot be involved in study design, data collection or interpretation of results. However, they can provide comments about protocols and formal scientific advice through existing regulatory processes. They also said that it will be important that it is clear who is responsible for the quality of the data/results generated in PPCs/PPPs.

Academics said that, although they would be interested to participate in PPCs/PPPs, they are concerned about the possible negative consequences of a perceived loss of 'independence', and the risk to their reputation. The consequences could limit their possibility of providing independent expertise to organisations such as EMA and WHO. Many researchers working in these organisations are also lecturers/professors and in this context they have a responsibility to be seen to be providing independent student training. The CROs said that being involved in PPC/PPP could lower their probability of success for public sector tenders because of the association with the private sector.

Sometimes when results from a PPC/PPP study are presented, some people, both healthcare professionals and the general public, are almost automatically mistrustful. Some of

these people systematically do not believe that studies results can be trustable if MAHs have participated. It will be important for MAHs and other stakeholders in PPCs/PPPs to communicate more transparently about how studies are funded, not only to professional audiences but also to the general public to gain professional and public trust.

All stakeholders generally have multiple CoIs, which are not only financial. CoIs must be declared by everyone involved and what these mean should be clearly explained to the general public to improve public trust. Not all CoIs have negative impact on the project. Some are only perceived as CoIs and may not have any impact on the study conduct However, they must be declared in the interest of transparency and ethics. The WHO has developed a guidance based on a risk assessment approach to manage converging and conflicting interests when developing partnerships with non-State actors.[12] In the NGO governance model, public trust issues associated with funding from industry are addressed by working with several companies who provide funds that are not earmarked, allowing the NGO to decide independently how these funds are allocated. This is similar to the role of trustee developed in the ADVANCE governance models and could support trust in vaccine B/R PPCs/PPPs projects.

The general public expect marketed vaccines to be safe, so it is difficult for them to understand why vaccine B/R monitoring is needed, therefore we need clear communication (and education) around this topic. The PHIs also expressed fear of loss of scientific and societal trust if they were participant in PPCs/PPPs, and this mistrust could have a negative impact on the success of vaccination programmes. Since the determinants of public trust are varied, and can be context-specific it will be important for future PPCs/PPPs to provide communication based on joint and structured strategies.

Trust between participating stakeholders within a PPC/PPP and trust between non-participating stakeholders and the PPC/PPP have been shown to have a positive effect on innovative outcomes, and on the overall performance of the project. A transparent process, based on open communication, information sharing and shared decision-making can increase the level of support for PPCs/PPPs, Consistent, timely and proactive (not reactive) communication is primordial to help build trust, particularly for non-participating stakeholders. However, it is generally acknowledged that public trust in institutions/organisations is decreasing worldwide, due to various confidence crisis in the healthcare setting as well as other settings.

Sustainability: towards a European platform?

Although it was not the purpose of the workshop to discuss the technical aspects of the sustainability of ADVANCE or another structure for European vaccine benefit/risk monitoring studies, there was some discussion on this. One approach that was mentioned was to have a common European data platform, so that data would be available in a common format to overcome the difficulties associated with the heterogeneous formats of the data collected

[12] http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_R10-en.pdf?ua=1

nationally. Even if the data collection is different, it would be useful to work together to define a set of 'essential data' that could be collected so as to make the data more sharable (e.g. the Findable, Accessible, Interoperable and Re-usable (FAIR) principle).[13]

To make a European platform to be sustainable, some countries would have to participate, but the vaccination programmes are different with not all vaccines included in all schedules. For example, the UK is the only country that includes the herpes zoster vaccine, and for other vaccines (e.g., influenza vaccine) that are included in >1 country, there are different age groups and/or target populations. The existence of suitable governance models, that can be adapted to a given situation, when needed, will not be enough to ensure sustainability. Sustainability also requires adequate levels and length of funding. For example, an independent funding mechanism could be developed to allow MAHs and PHIs to indirectly fund studies. Having a trustee who is responsible for collecting and allocating funding is a possible solution to this problem. One working example of this is EurVacc, which is dedicated to HIV vaccine studies.[14] For vaccine B/R studies, one existing structure that could the decision-maker is the ECDC who could work with the PHIs who would be responsible for implementation/management.

Legal considerations

During the workshop legal considerations in the EU countries were discussed by a specific group of legal experts from different stakeholders groups and countries through a dedicated breakout session.

During the legal experts' workshop and plenary discussion on Day 1, some vaccine MAHs said that the involvement of competitors (i.e. other vaccine manufacturers) in the study could make the collaboration difficult, in terms of company policies. PHIs said they would be more comfortable if more than one MAH was involved. The legal experts from The Netherlands said that, in their country, studies could be considered as interfering with free-market competition if not all interested stakeholders, including the MAHs are involved.

Each stakeholder has their own vested interests which may be difficult to overcome. It was also said that the sharing of data with industry, collected by PHIs with limited informed consent, could present a legal hurdle. However vaccine MAHs can need access to the data to fulfil their legal obligations. In general, it was felt that freedom of information acts and data protection laws and the European General Data Protection Regulation (GDPR) should be taken into consideration in all PPCs/PPPs.

The concern about data and results ownership was raised by the legal experts. Generally for vaccines, PHIs own the original data that they collect. However, the ownership of the results produced within these PPCs/PPPs need to be discussed on a case by case basis. Various solutions could be envisaged, including co-ownership of results, but this should be clearly defined in the project/study contract and agreed between stakeholders before the project is

[13] https://www.force11.org/group/fairgroup/fairprinciples
[14] http://www.eurovacc.org/

initiated. Who has the right to use the data is another important question. Generally, whole databases are not shared with non-owners who want to analyse certain data; an analysis data set, containing the data required to answer the study question(s) is usually extracted for analysis, QC and archiving. The rules governing data sharing should be included in the study/project contract, making clear what can and cannot be done.

The question of dissemination of results was also addressed. If the study is performed in the setting of a public health emergency, the PHI(s) would need to make the results public as soon as possible. Challenge is to balance the PHIs need for quick data with MAHs need to have SOP-compliant (fully quality controlled data).

Despite the various questions discussed the legal experts agreed that there are no hard legal barriers to develop vaccine B/R PPCs/PPPs in Europe.

7. General conclusions

The following general conclusions were developed by the ADVANCE Governance Group after the meeting, based on the discussions during the meeting.

The meeting provided a unique forum for open and interactive discussions between various stakeholders about their ideas and concerns on how organisations from the public and private sectors can collaboration and participate in the development of a future sustainable framework for vaccine B/R monitoring in Europe. The participants at the meeting showed different levels of acceptability of the ADVANCE governance models for PPCs/PPPs and it was clear that no one model will fit all situations, and that models will have to be adaptable to answer different research questions and in specific contexts in the particular real-life setting of the vaccine B/R studies.

8. Recommendations for governance guidance

It is crucial to emphasise the added-value for stakeholders to use a collaborative governance model, particularly for PHIs, but also for other stakeholders. This can be demonstrated by putting into perspective different potential research questions and taking into consideration the impact at the European level. The development of collaborative projects should be perceived by both public and private stakeholders as going much beyond just providing access to data or funding.

It is important to present the available governance materials to the target audiences (scientific experts and organisations willing to develop collaborative projects for vaccine B/R assessment and monitoring). The ADVANCE framework will propose a generic governance model with options allowing adaptations for project-specific issues and context. Providing pertinent examples of how this could work in different settings will be an essential part of the communication strategy. It will probably be helpful to include communication about the similarities between the ADVANCE model and the NGO model to help a larger audience to understand and support the proposed ADVANCE governance framework.

A key challenge that needs to be addressed is the fact that PHIs need strong safeguards to prevent non-scientific interests of private partners being influential, or at least being perceived to be influential. To address this challenge, the ADVANCE framework will propose a generic governance model with options allowing adaptations for project-specific issues and context. Providing pertinent examples of how this could work in different settings will be an essential part of the communication strategy.

In addition, we propose to reinforce confidence between stakeholders in PPC/PPP and between the PPC/PPP and the public. This could be facilitated by developing clear definitions for the roles and responsibilities of those involved in decision-making about the study design, conduct, analysis and reporting, transparency measures, funding transferred to third parties, and public declaration of interests. Active participation of patient associations and civil society organisations will be sought to reassure and contribute to the development of public trust in these projects.

We need to acknowledge that trust is built with a series of proofs and takes time. All PPC/PPP processes will include a high level of traceability for documents review. A defined risk assessment approach to manage CoIs, based on the WHO guidance, will be included in these processes. The ADVANCE Code of Conduct will be used for the conduction of vaccine B/R studies.[15]

We should also ensure appropriate communication strategies about PPCs/PPPs for all participating and non-participating stakeholders to ensure that the aims, goals, benefits and the different stakeholders' responsibilities in the project are clear to support the legitimacy of the collaboration/partnership and ensure trust in results.

[15] 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(15):1844-55

9. Recommendations for the ADVANCE project

ADVANCE should communicate more about the added value of PPPs within and outside the project, with specific communication strategies for different targeted audiences. We should strive to develop proactive communication strategies with simple but accurate messages. It will also be essential to have consensual communication about issues where there are divergent opinions. Some stakeholders think it is important to recognise that the primary role of the ADVANCE project is to communicate to healthcare professionals not to the public. However, these professionals should then have the means to cascade communication to the general public. Other stakeholders feel that clear, accurate communication to the public is important in building and maintaining public trust.

ADVANCE could learn more lessons from other terminated and on-going PPPs, in terms of communication.

To address questions about public trust in PPCs/PPP, some of the workshop participants suggested that ADVANCE should conduct an extensive literature review or a large survey to identify the determinants or seek synergy with other expert groups. This work was not envisaged in the initial ADVANCE work programme and recommendations for the Communication strategy regarding PPCs will be included in Deliverable 1.12 *"Developing communication strategies on vaccine benefit and risk: Guidance for public-private collaborations."* [16]

[16] An ADVANCE workshop on communication of risk-benefits of vaccines was organised on 29 June 2017 at the London School of Hygiene & Tropical Medicine (LSHTM). Its objective was to agree on the format and content of a practical guidance document (to be submitted as Deliverable 1.12) with step-by-step recommendations addressing various scenarios where communication is critical.

10. Next steps

A white paper,[17] integrating input from this workshop will be prepared for submission to IMI and ECDC by end of September 2017. The governance guidance that has been developed by ADVANCE will then be made publically available. A manuscript will be prepared for publication to a peer-reviewed journal.

ECDC will write a blueprint[18], based on workpackage ouptuts , to discuss the feasibility and sustainability of ADVANCE's proposals for real-life settings and examine the future perspectives for PPCs/PPPs for vaccine benefit-risk monitoring studies in Europe. This blueprint, which is the final ADVANCE deliverable, will be available in September 2018, at the end of the project.

[17] A white paper is a document that should inform readers about complex issues and summarise the issuing body's viewpoint on the issues in a concise manner. It can help readers understand the issues, solve problems, or make decisions. This white paper will inform the vaccine scientific community about governance issues and summarise ADVANCES recommendations.

[18] A blueprint is an architectural plan or set of proposals that outlines something is expected to work