



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

Grant Agreement n°115557

Good Practice Guidance

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

Deliverable 1.9

Guidance on best practices – Modules 1 and 3

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	Good Practice Guidance – Modules 1 and 3: Code of Conduct and Quality recommendations		
	WP1. Best practice and code of conduct for benefit-risk monitoring vaccines		Version: V2 Final
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Description of the deliverable	This deliverable aims to propose guiding principles for the ADVANCE Code of conduct (Module 1) and Quality management (Module 3) as part of the Good practice guidance. Module 2 (Governance models) and Module 4 (Communication recommendations) are submitted separately as specific Deliverables (D1.4, D1.10 and D1.12).
Key words	Guiding principles, code of conduct, quality management.


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Xavier Kurz and Vincent Bauchau	July 2016		Finalisation of draft Code of Conduct (version for publication) and circulation to WP1 WG1 and Steering Committee
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DEFINITIONS

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


- **AEMPS.** Agencia Española de Medicamentos y Productos Sanitarios (Spain)
- **ASLCR.** Azienda Sanitaria Locale della Provincia di Cremona (Italy)
- **AUH.** Aarhus Universitetshospital (Denmark)
- **CRX.** Crucell Holland BV (Netherlands)
- **ECDC.** European Centre for Disease Prevention and Control (Sweden)
- **EMA.** European Medicines Agency (United Kingdom)
- **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands) - Coordinator
- **GSK.** GlaxoSmithKline Biologicals, S.A. (Belgium) – EFPIA Coordinator
- **KI.** Karolinska Institutet (Sweden)
- **LSHTM.** London School of Hygiene and Tropical Medicine (United Kingdom)
- **MHRA.** Medicines and Healthcare products Regulatory Agency (United Kingdom)
- **NOVARTIS.** Novartis Pharma AG (Switzerland)
- **OU.** The Open University (United Kingdom)
- **P95.** P95 (Belgium)
- **PEDIANET.** Società Servizi Telematici SRL (Italy)
- **PFIZER.** Pfizer Limited (United Kingdom)
- **RCGP.** Royal College of General Practitioners (United Kingdom)
- **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu * National Institute for Public Health and the Environment (Netherlands)
- **SP MSD.** Sanofi Pasteur MSD (France)
- **SP.** Sanofi Pasteur (France)
- **SSI.** Statens Serum Institut (Denmark)
- **SURREY.** The University of Surrey (United Kingdom)
- **SYNAPSE.** Synapse Research Management Partners, S.L. (Spain)
- **TAKEDA.** Takeda Pharmaceuticals International GmbH (Switzerland)
- **UNIBAS.** Universitaet Basel (Switzerland) - **Managing entity of the IMI JU funding**
- **UTA.** Tampereen Yliopisto (Finland)
- **WIV-ISP.** Institut Scientifique de Santé Publique (Belgium)
- **Analytical dataset.** The minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.

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- **Consortium.** The ADVANCE Consortium, comprising the above-mentioned legal entities.
- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ADVANCE project (115557).
- **Primary data collection.** Data collection directly from healthcare professionals or consumers (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care).
- **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.
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Secondary data collection:** Secondary use of data previously collected from consumers or healthcare professionals for other purposes and where all the events of interest have already happened. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. Study designs may include case-control, cross-sectional, cohort or other study designs making secondary use of data.
- **Start of data collection.** The date from which information on the first study subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
- **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.

List of abbreviations:

- B/R: Benefit-risks
- CoC: Code of Conduct
- DoI: Declaration of Interests
- EC/IRB: Ethics committee/Institutional Review Board
- EMA: European Medicines Agency
- ENCePP: European Network of Centers Centres for Pharmacoepidemiology and Pharmacovigilance
- EU: European Union
- GCP: Good Clinical Practice
- GPG: Good Practice Guidance
- GVP: Good Pharmacovigilance practice
- HCP: Health Care Professional
- ISO: International Organization for Standardization
- MAH: marketing authorisation holder
- PAS: Post-Authorisation Study
- PASS: Post-Authorisation Safety Study
- POC: Proof-of-Concept study
- QM: Quality management

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- SAP: Statistical Analytical Plan
- STROBE: STrengthening the Reporting of Observational studies in Epidemiology

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EXECUTIVE SUMMARY

Introduction

Effective collaboration between stakeholders and governance for the conduct of studies are among the main objectives of ADVANCE. In this context, Work Package 1 will deliver a good practice guidance including core values to be integrated in this framework, models for interactions, principles of governance between public private stakeholders and minimum quality criteria as components of a sustainable, transparent and high quality organisation of vaccine studies and trust into vaccination programmes. A communication strategy will be informed by structured information on the population's perceptions on vaccines and immunisation programs.


The good practice guidance (GPG) is divided into four modules covering different aspects:

- Module 1: Code of Conduct
- Module 2: Governance models
- Module 3: Quality management
- Module 4: Communication recommendations.

This Deliverable 1.9 "Guidance on best practices-draft" includes Module 1 and 3. Module 2 is submitted in parallel as Deliverable 1.10 "Final conceptual model for public private interactions" and two elements to be integrated in Module 4 are submitted separately as Deliverable 1.7 "Analysis of key issues and gaps about perception and knowledge on benefits and risk of vaccines" and Deliverable 1.12 "Strategy for public communication in the context of vaccine benefit-risk monitoring".

Although this is considered a "final" good practice guidance, there will be further opportunities for their review and improvement They include:

- Submission of the Code of conduct in a peer review journal; this submission will give the opportunity to receive comments from reviewers external to the project, and the dissemination of the text, if accepted for publication, will stimulate further discussions.
- Further work will be performed on the Governance models including the development of a research contract template for each governance model, consultation of wide range of stakeholders, including layers and a workshop to be organised by IMI with a large range of stakeholders.
- Quality aspects have been introduced in the proof-of-concept studies and will be subject to a review of their implementation and of any concerns that may be associated with their use in terms of resources. A public consultation will be considered by the ADVANCE consortium.
- Results from the ADVANCE work on Communication recommendations will be submitted for publication. As the objectives of this work include the development of a strategy on how to communicate results of studies of vaccine, the communication recommendations will be applied to the results of the POC studies and tested with the public, patient representatives and health care professional representatives.
- All four modules will be submitted to WP7 for their review of the implementability by an external advisory group.

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The final outcome of the group will be a guidance to be integrated in the Blueprint, which is the final deliverable of ADVANCE.

Module 1. The Code of Conduct

Lessons learnt from the 2009 (H1N1) flu pandemic showed that factors limiting the capacity to collect European data on vaccine exposure, safety and effectiveness include lack of rapid access to available data sources or expertise, difficulties to establish efficient interactions between multiple stakeholders, lack of confidence between private and public sectors, concerns about possible or actual conflicts of interest (or perceptions thereof) and inadequate mechanisms for public funding of studies. ADVANCE was established to create a reliable, valid and tested framework providing scientific evidence on vaccine benefits and risks in Europe, including a code of conduct (CoC) and governance for multi-stakeholder interactions in collaborative studies.

The development of the CoC was guided by three core values (Best science, Strengthening public health and Transparency) and a review of existing guidance and relevant published articles.


The CoC includes 50 recommendations in 10 topics (Scientific integrity, Scientific independence, Transparency, Conflicts of interest, Study protocol, Study report, Publication, Subject privacy, Sharing of study data, Research contract). For each topic, it includes a definition, a set of recommendations and a list of additional reading.

The concept of the study team is introduced as a key component of the CoC with a core set of roles and responsibilities.

It is hoped that voluntary adoption of the CoC by all partners involved in a study will facilitate and speed-up its initiation, design, conduct and reporting by avoiding lengthy discussions on the principles of collaboration under which the study will be conducted. Adoption of the CoC should be stated in the study protocol, study report and publications and journal editors are encouraged to use it as an indication that good principles of public health, science and transparency were followed throughout the study.

Module 3. Quality recommendations

Key aspects to be addressed by a future framework for vaccine benefit-risk monitoring that have been identified included "Quality assurance and quality control". Quality of research requires a set of activities aimed to direct, control and coordinate quality – i.e. Quality management (QM). QM is a continuum of activities that aim to prevent, detect, correct, control errors. An overview of elements of essential quality management activities was deemed useful to promote quality, facilitate rapid implementation of research. A review was conducted for commonly referred good practice guidelines and regulatory guidance applicable to observational research for the elements of quality control and assurance. The current guidance provide limited description of the aspects of quality assurance through written procedures and governance around them, as well as the organisational conditions and the active planning of quality control procedures through monitoring, (self) audit and their resulting actions that ensures a continuous improvement cycle. A baseline inventory of the current status of implementation of elements of quality control and assurance among the ADVANCE stakeholders likewise showed a gap

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for the same type of elements of quality management. The Quality Module embedded in this deliverable provides an overview of the elements of essential quality management activities. This overview will serve for the evaluation of the implementation of good quality practices in the proof-of-concept studies. The final result will be an implementable guidance on quality management for observational research endorsed by all stakeholders in the ADVANCE Blue Print.

Discussion

The aim pursued by ADVANCE in the development of good practice guidance is to provide standard principles by which studies initiated, managed or sponsored by academic institutions, public health authority or vaccines will be conducted through the ADVANCE infrastructure, either directly or via third parties.


Of the four Modules included in this Deliverable, three were planned at the start of the project (Code of conduct, Governance models, Communication recommendations). Recommendations on quality management were added based on comments received from patients' and health care professionals' representatives who suggested that having confidence in the quality of the study would be an important element for them to have confidence in its results. The approach to provide recommendations on the quality aspects of studies which should be considered "minimum good practice" was adopted in order to support their adoption by research centres.

The four modules contained in the good practice guidance were developed separately. They need further work in terms of consultation, testing and review by the ADVANCE WP7 as to their implementability and feasibility.

In addition:

- It is planned to submit the Code of conduct in a peer review journal (e.g. Vaccine); this submission will give the opportunity to receive comments from reviewers external to the project, and the dissemination of the text, if accepted for publication, will stimulate further discussions.
- Further work will be performed on the Governance models including the development of a research contract template for each governance model, and a workshop to be organised by IMI with a large range of stakeholders.
- Quality aspects have been introduced in the proof-of-concept studies and will be subject to a review of their implementation and of any concerns that may be associated with their use in terms of resources. A public consultation will be considered by the ADVANCE consortium.
- Results from the ADVANCE work on Communication recommendations will be submitted for publication. As the objectives of this work include the development of a strategy on how to communicate results of studies of vaccine, the communication recommendations will be applied to the results of the POC studies and a "mock-up" communication of these results and how they were obtained will be tested with the public, patient representatives and health care professional representatives.

The four Modules of the good practice guidance will be ultimately integrated in the final ADVANCE Blueprint.

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1. INTRODUCTION

The recent pandemic influenza vaccines experience highlighted many issues in the way the current post-marketing monitoring system for vaccines is functioning in Europe and what could be improved. Several factors limited the capacity to collect European data on vaccine exposure, safety and effectiveness, including:

- the lack of rapid access to available data sources, expertise or willingness;
- the difficulty to establish efficient interactions between multiple stakeholders (regulators, public health agencies, vaccine manufacturers);
- the lack of confidence/trust between private and public sectors;
- concerns about possible (perception of) conflicts of interests;
- disharmonised communications;
- lack of mechanisms allowing the funding of studies.


Although these observations were made in the context of the pandemic influenza vaccines, they are also relevant for other marketed vaccines including MMR, DTaP, Rotavirus, Pneumococcal, HPV vaccines.

On the other hand, a few successful projects demonstrated the potential for effective collaborations in Europe:

- the Vaccine European New Integrated Collaboration Effort (VENICE) project collected coverage information through web-based surveys across all the EU/EEA Member States for ECDC to support monitoring at national and EU level;
- the Influenza - Monitoring Vaccine Effectiveness (I-MOVE) consortium utilised various methods including cohort studies and case-control studies based on sentinel and other surveillance with laboratory confirmation, publishes harmonised protocols that are regularly updated, facilitates standard approaches and allows for meta-analysis and replication of I-MOVE data;
- the VAESCO consortium demonstrated the usefulness of a collaborative federated database-driven approach in the EU for assessment of vaccine safety. This effort translated the experience of the US Vaccine Safety Datalink.

To address limitations in the current capacity for conducting rapid vaccine benefit-risk monitoring activities, the ADVANCE project was initiated with the vision to deliver best evidence at the right time to support decision-making in Europe. Its mission is to establish a validated and tested best practice framework to rapidly provide robust data on vaccine benefits and risks to support accelerated decision making throughout the life cycle of vaccines. For this purpose, it needs to fulfil the needs of different target groups and stakeholders (e.g. national authorities, insurance companies, regulatory agencies, public health agencies, vaccine manufacturers, health care providers, consumers, etc).

Effective collaboration between stakeholders and governance for the conduct of studies are among the main objectives of ADVANCE. In this context, Work Package 1 will develop a good practice guidance including core values to be integrated in this framework, models for interactions, and principles of

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governance between public private stakeholders that might be utilised to build a sustainable, transparent and high quality organisation of vaccine studies and trust into vaccination programmes. A communication strategy will be informed by structured information on the population's perceptions on vaccines and immunisation programs.

Deliverable 1.6 of ADVANCE consisted in a draft of the Good of Practice Guide (GPG). This deliverable provides a development of the Guide. As explained below, the GPG contains four Modules which have been developed separately. They are also submitted in parallel as distinct deliverables (D1.7, D1.10 and D1.12). These deliverables are expected to be further discussed and amended in the ECDC's implementability and feasibility analysis as well as, for D1.10, through a comprehensive legal review, they are not physically included in this document. This document includes the ADVANCE Code of Conduct presented as a manuscript to be submitted for publication (Module 1) and the draft quality recommendations (Module 3), which is tested in the Proof-of-Concept studies.

2. Objectives of the Good Practice Guidance

An objective of ADVANCE is to propose a good practice guidance for vaccine benefit-risk monitoring activities that can be used as a reference for the planning, initiation, design, conduct and reporting of rapid post-marketing vaccine benefit-risk monitoring activities. Ultimately, the guidance will be adopted by the main stakeholders concerned by such activities following a broad consultation.

To achieve its objectives, this guidance aims to:


1. be practical and address key aspects that represented stumble blocks in the past, including funding aspects, content of research contracts, ethical issues, interactions between involved stakeholders;
2. be agreed by all stakeholders;
3. be sustainable, namely propose solutions that could be applied after the ADVANCE project and be accepted by organisations beyond those involved in ADVANCE;
4. be tested in real-life situations through Proof-of-Concept studies;
5. take into account different situations and different needs and requirements of involved stakeholders for a given study.

3. Structure of the Good Practice Guidance

The good practice guidance is divided in four modules covering different aspects:

- Module 1: Code of Conduct
- Module 2: Governance models
- Module 3: Quality management
- Module 4: Communication recommendations.

Module 1 (Code of Conduct) is included in this Deliverable 1.9. A draft version of the Code of Conduct was presented in Deliverable 1.6 in May 2015. Since this date, it has been further reviewed by WG1, published for public consultation from 29 September to 15 November 2015

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and further amended based on the comments received following the public consultation. The text of Module 1 of this Deliverable therefore presents the revised ADVANCE Code of Conduct in a format based on a manuscript that will be submitted as a Review article to the journal “Vaccine”, with the addition of the main results of the public consultation. A compilation of the comments received during the public consultation is presented in Annex 1. The text of Module 1 does not include the sections on Guiding principles and Methods that were fully described in Deliverable 1.6 published on the ADVANCE website.¹


The text of the Code of Conduct presented in this Deliverable is therefore not “final” as the text will benefit from comments expressed by reviewers of the journal(s) where it will be submitted for publication and from the reviewers nominated by the ECDC for the implementability evaluation to be performed by ADVANCE WP7. It is also intended to publish it in electronic format on the ADVANCE website and to amend it as needed based on comments received.

Module 2 (Governance models for public-private interactions) is presented in parallel as Deliverable 1.10 “Final conceptual model for public-private interaction”. It is therefore not included in this document. Furthermore, it will be submitted to ADVANCE WP7 to be analysed for its implementability and, in the same time, will undergo a thorough legal review at the level of various stakeholders (e.g. vaccine manufacturers, public health institutes, EMA). Additional components will also be developed such as templates for research contracts. Discussions will then take place within ADVANCE on how it will be disseminated and finally included in the Blueprint.

Module 3 (Quality management) is a module that was added in the course of the ADVANCE project and should also still be considered as a draft. The main provisions of the recommendations on quality management are being tested in the first round of proof-of-conduct studies and may be published for public consultation in Q4 2016. They are therefore not finalised. They will be included in the final document included in the Blueprint.

Module 4 (Communication recommendations) contains D1.7 “Analysis of key issues and gaps about perception and knowledge on benefits and risks of vaccines”, and D1.12 “Strategy for public communication in the context of vaccine benefit risk-communication”. These two documents may not be considered as final, as comments will be received from the implementability analysis or in response to submissions for publication. In addition, the recommendations will be tested through a mock-up communication on the results of the Proof-of-concept studies.

¹ http://www.advance-vaccines.eu/app/archivos/publicacion/7/ADVANCE_WP1_Deliverable-1_6_V5-Final.pdf

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4. Module 1: ADVANCE Code of Conduct for Collaborative Vaccine Studies

4.1. Abstract

Lessons learnt from the 2009 (H1N1) flu pandemic showed that factors limiting the capacity to collect European data on vaccine exposure, safety and effectiveness include lack of rapid access to available data sources or expertise, difficulties to establish efficient interactions between multiple stakeholders, lack of confidence between private and public sectors, concerns about possible or actual conflicts of interest (or perceptions thereof) and inadequate mechanisms for public funding of studies. The Innovative Medicines Initiative's Accelerated Development of VAccine benefit-risk Collaboration in Europe (ADVANCE) consortium was established to create a reliable, valid and tested framework providing scientific evidence on vaccine benefits and risks in Europe, including a code of conduct (CoC) and governance for multi-stakeholder interactions in collaborative studies. The development of the CoC was guided by three core values (Best science, Strengthening public health and Transparency) and a review of existing guidance and relevant published articles. The CoC includes 50 recommendations in 10 topics (Scientific integrity, Scientific independence, Transparency, Conflicts of interest, Study protocol, Study report, Publication, Subject privacy, Sharing of study data, Research contract). For each topic, it includes a definition, a set of recommendations and a list of additional reading. The concept of the study team is introduced as a key component of the CoC with a core set of roles and responsibilities. It is hoped that voluntary adoption of the CoC by all partners involved in a study will facilitate and speed-up its initiation, design, conduct and reporting by avoiding lengthy discussions on the principles of collaboration under which the study will be conducted. Adoption of the CoC should be stated in the study protocol, study report and publications and journal editors are encouraged to use it as an indication that good principles of public health, science and transparency were followed throughout the study.

4.2. Introduction

The lessons learnt from the 2009 (H1N1) flu pandemic identified several factors limiting the capacity to rapidly collect and analyse post-marketing European data on vaccine exposure, safety and effectiveness. Issues included lack of rapid access to available data sources or expertise, difficulties to establish efficient interactions between multiple stakeholders (regulators, public health agencies, vaccine manufacturers), lack of confidence between private and public sectors, concerns about possible or actual conflicts of interest or perceptions of conflicts of interest, disharmonised communications and lack of mechanisms allowing the funding of studies. They also highlighted the need to establish an European infrastructure (networks, common methods, data-sharing) to timely assess the burden of vaccine preventable diseases, quickly evaluate safety signals, estimate the utilisation, benefits and risks of vaccines and promptly evaluate the effectiveness of public health measures [1-3]. In 2013, the Innovative Medicines Initiative established a public-private consortium, the Accelerated Development of Vaccine benefit-risk Collaboration in Europe (ADVANCE) [4], with the aim to establish a reliable, valid and tested framework providing rapidly robust data and scientific evidence on vaccine benefits and risks in Europe. To support effective collaborations and clear governance for the conduct of studies, ADVANCE developed a best practice guidance including a code of conduct, governance models, quality management and communication recommendations.

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Guidelines on the planning and conduct of pharmacoepidemiological studies already exist at national and international levels and were used as a starting point to develop the ADVANCE CoC, but it was considered that none of them was comprehensive enough to cover the needs for guidance for observational studies conducted on vaccines. This field has a number of key characteristics including focus on preventive health care, potentially large exposed populations in all age groups, a limited number of vaccine manufacturers, a broad range of concerned stakeholders (including public health authorities, regulatory authorities, vaccine manufacturers, academic institutions, health care professionals, vaccinated individuals and the public) and high attention to actual or perceived potential conflicts of interest. The Code of Conduct [5] published in 2010 by the European Network of Centres in Pharmacovigilance and Pharmacoepidemiology (ENCePP) has been a landmark document providing standards on transparency and scientific independence in pharmacoepidemiology. One of its main provisions being that no person with a financial, commercial or personal interest in a particular study outcome shall take part in any study activity once the protocol has been finalised, it does not provide guidance for the conduct of collaborative studies involving multiple partners during the whole research process (be they regulatory authorities, public health authorities, academic institutions or vaccine manufacturers). ADVANCE acknowledges that high quality studies may be performed thanks to the collaboration between different partners and these studies should also be guided by principles of good practice at every step of the study. ADVANCE aimed therefore to develop a CoC applicable to all collaborative studies.


4.3. Methods

In a first step, a survey was conducted among the ADVANCE consortium to assess what guiding values were considered the most important ones for the planning, initiation, design, conduct and reporting of post-marketing vaccine benefit-risk monitoring activities. Among the 14 values initially identified (science, ethics, improving public health, excellence, integrity, transparency, open dialogue, independence, partnership, trust, reliability, respect, accountability, commitment), those ranking first were ***best science*** (“benefit-risk monitoring should rapidly deliver the best evidence possible on the research questions, applying the appropriate scientific methods with integrity”), ***strengthening public health*** (“all decisions should be guided by the extent to which they help to improve health at individual and population levels”) and ***transparency*** (“key decisions and there rationale, the choice, design and conduct of the study, the interpretation of results, funding sources, roles of each participant and declarations of interests should be disclosed”) (information on this survey is available in a separate document) [6]. These values were used to identify the topics to be addressed in the CoC and develop recommendations.

In a second step, existing guidelines were identified and selected through consultation of ADVANCE consortium members, screening of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology [7], literature search and screening of the reference lists of retrieved documents. Relevant recommendations were extracted by at least two members of ADVANCE work package 1 and combined according to the pre-defined topics. For each topic, all recommendations were reviewed and either removed or kept and reworded as necessary. New recommendations were developed as needed.

4.3.1. Public consultation

The draft Code of Conduct was published on the ADVANCE website for public consultation from 29 September to 15 November 2015. Announcements were made on the EMA website, the ENCePP website,


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the IMI website and website of several partners. The following organisations were specifically contacted to inform them of the consultation:

- ACRO, USA
- ADELFI, France
- ADVANCE consortium
- ENCePP
- EMA committees: CHMP, HCPWG, PCWP, PRAC, VWP
- EBE, Belgium
- EFPIA, Belgium
- Epiconcept, France
- EUCOPE, Belgium
- EUCROF, Italy
- EUFEMED, Belgium
- European Institute of Women's Health, Ireland
- European Medical Information Framework (EMIF-IMI), Belgium
- EuropaBio, Belgium
- Europharm SMC, Belgium
- IMI, Belgium
- ISoP, UK
- ISPE, USA
- The Standing Committee of European Doctors (CPME), Belgium
- Vaccines Europe, Brussels

Comments received were collected and compiled by the European Medicines Agency. They originated from 20 organisations and individuals from 9 countries:

- Chandrakant Lahariya, individual opinion, India
- CPME, Belgium
- Department of Pediatrics, Rutgers - New Jersey Medical School, USA
- EMIF-IMI, the Netherlands
- ENCePP Italian Node, Italy
- ENCePP Working Group Independence and Transparency, UK
- European Institute of Women's Health, Ireland
- Gillian Hall Centre, UK
- GSKBio, Belgium
- Harvard Medical School, Department of Population Medicine, Boston, MA, US
- International Patient Organisation for Primary Immunodeficiencies (IPOPI), Belgium
- IRD, France
- Ivan Edelberto Cuevas Valdespino Organisation, Instituto Finlay de Vacunas, BioCubaFarma, Cuba
- Maastricht University Medical Centre, the Netherlands
- Pfizer, US
- RegiSCAR, Germany
- Sanofi Pasteur, France

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- Sanofi Pasteur MSD, France
- Seqirus, the Netherlands
- University of British Columbia, School of Population and Public Health, USA

These organisations can be categorised as follows: academia (5), vaccine manufacturers (5), scientific institution (4), patients' associations (2), CRO (1), others (3). The list of all comments received is provided in Appendix 1. A total of 386 comments were received, including 38 general comments (not related to a specific section) and 348 specific comments distributed by section of the code of conduct as follows:

Background information for the consultation:	19
A. Introduction:	22
B. Guiding principles:	12
C. Recommendations	
1. Scientific independence:	46
2. Scientific integrity:	26
3. Transparency:	37
4. Conflicts of interest:	21
5. Study protocol:	56
6. Study report:	32
7. Publications and scientific communications:	31
8. Subject privacy:	3
9. Sharing of study data:	29
10. Research contract:	14

Many comments were editorial but the main ones on the content can be summarised as follows:

a) Why do we need this code of conduct?


- It is not clear why this document is necessary. There is nothing specific to vaccines in this document.
- Findings from the gap analysis are not sufficiently synthesised and/or highlighted.
- Further evidence as to why the existing guidelines are not sufficient should be provided.

b) Voluntary vs. compulsory code of conduct

- A code of conduct makes little sense as long as adherence remains voluntary.
- The code of conduct should become a systematic practice, integrated within a policy, for all the studies within the same institution.
- There is an apparent contradiction between adoption on voluntary basis and "shall" statements.
- The code of conduct should lead to an « ADVANCE stamp » on study reports.

c) Contradiction or confusion with the ENCePP code of conduct

- The ADVANCE code of conduct contradicts the ENCePP CoC provisions which requires that any party with a financial, commercial etc. interest cannot be part of the research team.

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- The document should not be called a 'code of conduct' to avoid confusion with the ENCePP CoC; it is rather a 'good practice guidance on scientific integrity in collaborative studies'.

d) Transparency

- The ADVANCE code of conduct requires a higher level of transparency than usual.
- The timing for the disclosure/publication of documents is not clear.
- Feasibility (transparency may require resources not available in smaller organisations).
- Need to specify exactly where to publish information.
- Concerns with intellectual property.

e) Conflicts of interest

- How would management of conflicts of interest be done practically.
- Who will decide (and how) that a potential conflict of interest is acceptable?
- Adherence to principles and measures of the CoC in itself may provide sufficient and appropriate measures to manage conflict of interest.

f) Study teams

- Clarify the concept of "autonomy" of members of the study team.
- How is the study team composition decided? Is it sponsor initiated or investigator initiated, and are scientists from companies part of the team?
- What are the explicit criteria for the qualifications and experience of the scientists involved in the study team?

g) Regulatory obligations

- Explain the obligations of the Good pharmacovigilance practice.
- A specific section of the protocol should make reference to the regulatory obligations and recommendations applicable to the study, with a rationale.


h) Other suggestion

- Describe the methodology used to draft the CoC.

These comments were discussed during the ADVANCE WP1 workshop that took place at the EMA on 10-11 December 2015. They were further addressed in a meeting of the WG1 drafting group on 28 January 2016 in Brussels. A revised version of the CoC was presented at the WP1 workshop held during the ADVANCE General Assembly meeting of 21-22 April 2016, further amended based on comments received from WP1 members and recirculated for final comments in July 2016.

4.4. Results

The ADVANCE Code of Conduct includes 50 recommendations in 10 topics: Scientific integrity, Scientific independence, Transparency, Conflicts of interest, Study protocol, Study report, Publication, Subject privacy, Sharing of study data, Research contract (Appendix 1). For each topic, the CoC

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includes a definition, a list of recommendations and a list of source guidelines or publications supporting the recommendations and suggested as additional reading. The text makes a difference between what is considered as requirements ("must") or recommendations ("should"). In case of public health crisis requiring rapid conduct of a study, investigators may focus on recommendations with a "must" clause.

The concept of the study team has been elaborated as a key component of the ADVANCE Code of Conduct with a core set of roles and responsibilities (Appendix 2). A study team should be established at the initiation of each study with the mandate to ensure that decisions taken during the study follow two key principles: scientific integrity - to ensure the highest quality of evidence is generated by the study – and transparency - to allow stakeholders, within or outside the study team, to assess the background and reasoning for the decisions taken. The Code of Conduct and its implementation at different steps of a study can be part of a structured monitoring of the study by external bodies such as scientific committee or ethical committee.

4.5. Discussion

Investigating benefits and risks of vaccines is both a complex and critical activity that involves multiple participants. Decisions to be made at the planning stage include definition of research objectives, specification of research outcomes, initiation of collaborations, allocation of resources, composition of teams, definition of roles and responsibilities, agreement on study designs, data sources, statistical plan, quality requirements and timelines, and processes for agreeing on the interpretation and reporting of the results. This can be particularly challenging where very rapid action needs to be taken and a (updated) benefit/risk assessment is needed with great urgency. Guiding principles may provide a solid foundation for these multiple decisions and the involvement of stakeholders. The principles of best science, strengthening public health and transparency have been adopted by the ADVANCE consortium to form the backbone for the development of a detailed, comprehensive and stand-alone set of recommendations aiming to facilitate collaboration between multiple partners of collaborative studies in the field of vaccine benefit-risk monitoring. The ADVANCE CoC was developed and agreed by a wide range of different organisations, including regulatory and public health authorities, vaccine manufacturers and academic organisations. It is therefore hoped that its voluntary adoption by all partners involved in a study will facilitate and speed-up its initiation, design, conduct and reporting by avoiding lengthy discussions on the principles of collaboration under which the study will be conducted. It is also recommended that adoption of the ADVANCE CoC should be stated in the study protocol, study report and publications and journal editors are encouraged to use it as an indication that good principles of public health, science and transparency were followed throughout the study. Whilst the ADVANCE CoC should be adopted voluntarily, it should be adopted entirely and by all individuals and organisations involved in the study and it should be applied provided that compliance with the applicable regulatory requirements and legislation can be maintained.


By including 50 recommendations, the ADVANCE CoC is a comprehensive but complex document, or can be seen to be complex, and this complexity may represent a limitation for its adoption in studies with few participants and simple procedures. We are convinced, however, that its principles are universal and could be applied not only to studies on the benefit-risk of vaccines but also to many other activities requiring collaborations such as drug safety or effectiveness studies. The experience will show whether it will contribute to the facilitation of vaccine studies by improving interactions between partners, supporting access to observational data sources and increasing confidence in their results. The

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ADVANCE Code of Conduct will be published on the ADVANCE website (www.advance-vaccine.eu) and be updated regularly based on comments received.

4.6. References

- [1] Pandemic report and lessons learned. Outcome of the European Medicines Agency's activities during the 2009 (H1N1) flu pandemic. European Medicines Agency (EMA/221017/2011), 29 April 2011.
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/04/WC500105820.pdf
[accessed 03.08.16]
- [2] Kurz X, Domergue F, Slattery J, Segec A, Szmigiel A, Hidalgo-Simon A. Safety monitoring of Influenza A/H1N1 pandemic vaccines in EudraVigilance. Vaccine 2011;29(26):4378-87
- [3] Wijnans L¹, de Bie S, Dieleman J, Bonhoeffer J, Sturkenboom M. Safety of pandemic H1N1 vaccines in children and adolescents. Vaccine 2011;29(43):7559-71
- [4] The Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE), <http://www.advance-vaccines.eu/> [accessed 03.08.16].
- [5] ENCePP. ENCePP Code of Conduct, http://www.encepp.eu/code_of_conduct/index.shtml; 2014 [accessed 03.08.16].
- [6] ADVANCE. Good Practice Guidance Module 1: Code of conduct. WP1 – Best practice and code of conduct for benefit-risk monitoring of vaccines. Deliverable 1.6 Guidance on best practices draft, Section 4.2, Version 5 Final, http://www.advance-vaccines.eu/app/archivos/publicacion/7/ADVANCE_WP1_Deliverable-1_6_V5-Final.pdf; 2015 [accessed 03.08.16].
- [7] ENCePP. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Revision 5, http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml; 2016 [accessed 03.08.16].

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4.7. Appendix 1. The ADVANCE Code of Conduct

4.7.1. Scientific integrity

Definition

Scientific integrity means acting in accordance with the values of science, such as truthfulness, honesty and open reporting. [1]

Recommendations

1. All researchers of the study team must be qualified to fulfil their role in the study.
2. All researchers must act in accordance with the following core values:
 - honesty (conveying information truthfully and fulfilling commitments)
 - accuracy (reporting findings accurately and completely)
 - objectivity (letting the facts speak for themselves and avoiding improper bias).
3. The study team is responsible and accountable for the integrity and accuracy of its work. The study team must adhere to Good epidemiological practices[2] and Good pharmacoepidemiological practices[3] without exception. It must ensure that its work is performed objectively, using the most appropriate methodology. The research must be factual, transparent and designed objectively to appropriately answer the research question.


Additional reading: [4],[5],[6],[7],[8],[9],[10]

4.7.2. Scientific independence

Definition: Scientific independence means that all decisions on scientific aspects of the research are based on scientific grounds without undue influence of any financial, commercial, institutional or personal interest in a particular outcome of the research. These scientific aspects include the framing of the research question, its translation into a study design and the analysis, interpretation and dissemination of the research.

Recommendations

4. The study design, methods of data collection, data analysis, interpretation of the results, study report and publications must be based only on robust scientific criteria without undue influence of any financial, commercial, institutional or personal interest in a particular outcome of the research.
5. Autonomy of members of the study team for making scientific decisions related to epidemiological research within their own organisation should be documented.
6. Fulfilling the following recommendations is necessary to safeguard scientific independence, in particular:
 - Clear and transparent roles and responsibilities for each party as defined in the research contract, providing the study team with the responsibility for all decisions on scientific aspects of the study (study design, methods of data collection, data analysis, interpretation of the results, study report and publications) and allowing consultation of other parties on important study documents such as the study protocol, study report and manuscripts.

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- Peer-review process with external experts or an external advisory board for important study documents such as the study protocol and study report; comments should be made available to all parties involved in the study.
- Protocol posting on public website before study data collection or extraction commences.
- Disclosure of all funding sources, all affiliations and all roles in the study; declaration of interests provided by all members of the study team.

Additional reading: [3],[11],[12],[13],[14]

4.7.3. Transparency


Definition

Transparency means having study information accessible to those having an interest in the study results, either as individuals or representatives of a group.[15]

Recommendations

1. Every study must be registered in a publicly accessible database before the start of data collection or data extraction. Study registration should include the study protocol. [16]
2. Sources of research funding must be made public at the time of study registration, in the study protocol and in the presentations of results, whether they are presented orally or in writing. All financial and non-financial public and private supports for the study should be documented.
3. Declarations of Interests of the members of the study team and external advisory committee must be made available at an early stage of the study, regularly updated and disclosed in the study report and in publications.
4. All comments received on the study protocol and study report that may impact the study outcome must be documented and made available to members of the study team, the study requester and the study funder.
5. The final study report should be uploaded into the publicly accessible database where the study is registered.
6. After completion of the final study report, study information should be made available to researchers from outside the study team in a collaborative approach. Such information may include the detailed study protocol (e.g. codes used for exposure and disease identification), the statistical analytical plan, programming codes, detailed interim and final results generated in the study and all comments received on the study protocol and study report that may impact the study outcome. Provision of this information should be based on a written request stating the purpose of the request. See also topic Sharing of study data.
7. In case of primary data collection, the subjects who participated in the study or their representatives are entitled to receive the main study results and the interpretation thereof.

Additional reading:[3],[12],[17],[18]

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4.7.4. Conflict of interest

Definition

Conflict of interest means a professional or personal interest sufficient to potentially influence the exercise of one's judgment regarding any activity of a research project.

Financial and commercial interests are the most easily identifiable sources of conflicts of interest, but conflicts can occur for other reasons, such as professional interest, personal or familial relationships, academic competition or beliefs.

Recommendations

1. Actual or potential conflicts of interest must be identified and addressed at the planning phase of the study in order to limit any possible undue influence on its design and support the credibility of the study team and results. Perceptions of conflicts of interest are as important to be addressed as actual or potential ones. The research contract must include a description of the management of conflicts of interest.
2. The members of the study team should declare on a standard form all interests that may lead to potential conflicts. All Declarations of Interest must be made publicly available and must be updated in cases of a change.

Additional reading:[2],[12],[19]


4.7.5. Study protocol

Definition

Study protocol means a document containing the methodological details of the design, implementation, analysis, documentation and publication of the results of an epidemiological study.

Recommendations

1. A protocol must be drafted as one of the first steps in any research project. It should demonstrate:
 - the rationale for the study – that is, why the study should be conducted, given the current state of knowledge;
 - the appropriateness of the proposed methods for testing the stated hypothesis, the methodological choices and why some of the possible options may have not been relevant or feasible;
 - the feasibility of doing the study as proposed - that is, that the study can be completed successfully in the specified time and with the available resources;
 - that the investigator(s) have the ability and skills to conduct the proposed study and are aware of limitations in the design;
 - the provisions made to protect participants' personal data and meet legal requirements.
2. The study protocol must be developed by a team of persons with relevant expertise (i.e. clinical, epidemiological and statistical expertise and expertise on specific clinical or methodological aspects of the study; data privacy and ethics). The process for reaching an agreement on design options

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should be agreed beforehand between the different persons involved. Internationally-agreed guidelines should be consulted to ensure that all important aspects of the protocol have been covered.

3. The protocol must include a section with the ethical considerations involved and information regarding funding, institutional affiliations, potential conflicts of interest and actions taken for their management, data protection and any incentives for subjects. If applicable, the protocol must be approved by the relevant research ethics committee before the study commences.
4. The protocol must include a description of the contribution of each party to the study design, writing of protocol and the study work programme with information on milestones, data ownership, data access, study reports, publications and authorship. The protocol serves also as the reference document for contractual agreements between parties.
5. A specific section must describe the regulatory obligations and recommendations applicable to the study.
6. A detailed draft protocol must undergo independent scientific review by experts that did not participate to its writing and are not anticipated to be directly involved in the study as investigators. Their recommendations are not binding but should be made available.
7. The study protocol should be registered in a publicly accessible register before the start of data collection or extraction.
8. The protocol may be amended as needed throughout the course of the study. Amendments to the protocol after the study start must be documented in a traceable and auditable way including the dates of the changes and the rationale for the changes. Changes to the protocol that may affect the interpretation of the study must be identifiable and reported as such in the study report and should be considered when interpreting the findings. This includes additions or amendments to the objectives or endpoints after the study start. The rationale for the change(s) to the protocol should be recorded with the protocol amendments or provided upon request once the study results have been published.
9. Key statistical analyses must be described in the study protocol. A detailed statistical analysis plan must be finalised before the end of data collection or extraction.

Additional reading: [3],[12],[16],[20],[21]


4.7.6. Study report

Definition

Study report means a document presenting the rationale, objectives, methods and results of the study, the interpretation and discussion of the results, including their strengths and limitations, and providing conclusions arising from the study.

Recommendations

1. The following principles must be followed for reporting results:
 - Interpretation of results is the responsibility of the study team exploiting the data and should acknowledge potential sources of errors and limitations of the study. Sensitivity analyses should

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be conducted to examine the effect of varying the study population inclusion/exclusion criteria, the assumptions regarding exposure, potential effects of misclassification, unmeasured confounders, and the definitions of potential confounders and outcomes on the association between the a priori exposure of interest and the outcome(s).

- Important safety concerns, even if based purely on subgroup analyses, must be documented and evaluated appropriately.
 - Any deviations from the protocol or from the statistical analysis plan must be clearly documented in the report and a reasonable scientific explanation should be provided.
 - Additional analyses which are deemed necessary based on initial results (e.g. formation of new sub-groups based on knowledge of (initial) study results) must always be presented as such. They must not be used for the purpose of verifying or rejecting the primary hypotheses stated in the protocol but can be used to generate further hypotheses.
 - Intermediate results of the study, i.e. preliminary or partial findings, analyses and conclusions formulated by the study team prior to the completion of the study, should be presented or published only subject to a procedure agreed in advance. Significant intermediate results that may affect public health must be published rapidly, but their preliminary nature must be clearly stated.
 - Investigators should develop a plan to assess and handle missing and non-interpretable data. It is important to provide the percentage of missing data for key variables of interest.
 - Sources affecting data quality and strengths and limitations of the study must be described.
 - Sources of funding, affiliations and any potential conflicts of interest must be declared in the final report.
2. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement and other internationally-agreed guidelines should be consulted when analysing and reporting data.
 3. A draft study report should undergo independent scientific review by experts that did not participate to its writing and are not anticipated to be directly involved in the study as investigators. Their recommendations are not binding but should be made available.
 4. The study report or a summary of the results should be included in the publicly accessible study register where the study is registered.


Additional reading: [3],[12],[16],[22],[23],[24]

4.7.7. Publication

Definition

Publication means any kind of disclosure to the public in whatever form or support, such as but not limited to manuscripts, publications, abstracts, posters, slides, texts or presentations, whether oral or written.

Recommendations

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1. All study results must be made publicly available. They should be published as soon as possible in a peer-reviewed scientific journal. Presentations at meetings are not substitutes for publications in the peer reviewed literature. Authorship of publications must follow the rules of scientific publication set by the International Committee of Medical Journal Editors (ICMJE). All sources of funding, affiliations and conflicts of interest must be published along with the study results. Unless there is an urgent public health issue, the results of a study should undergo independent peer review before they are made public.
2. The research contract must allow the principal investigator and relevant study team members to publish the study results independently from the funding or data source. The requester/funder must be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. These non-binding comments should be made available.
3. In cases where the study is discontinued for any reason, any preliminary or partial results or conclusions should be presented or published and the results from a discontinued study must be identified as such.
4. Procedures must be put in place to rapidly inform regulatory and public health authorities of the results of the study, irrespective of the submission of a manuscript for publication.

Additional reading: [3],[16],[25],[26],[27]

4.7.8. Subject privacy

Definition


Privacy means the ability of an individual to be left alone, out of public view, and in control of information about oneself. [28]

Personal data are any information relating to an identified or identifiable natural person. An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to her/his physical, physiological, mental, economic, cultural or social identity.[29]

Recommendations

1. Privacy of study subjects in relation to personal data is a core principle of any medical research and divulcation of confidential personal data may have serious implications. In a study where personal/identifiable data are not needed or are not available (such as in a study with secondary data analysis), this should be stated in the protocol.
2. In case where personal data are collected or used in a study, the applicable legislation, in particular Directive 95/46/EC in Europe must be followed.

Additional reading: [14],[27],[29],[30]

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4.7.9. Sharing of study data

Definition

Analytical data set means the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.[16]

Recommendations

1. There should be an open and collaborative approach to sharing study data with persons from outside the study team. Data sharing will normally concern only the anonymised analytical dataset.
2. Data should be shared only after the study report has been finalised.
3. Sharing of study data must be based on a written request specifying the ground of the request, the nature of the data requested and a protocol on the analyses to be conducted. It is the responsibility of the study team to verify the compliance of the request with the data protection legislation and to seek approval or ask advice from concerned persons or committees, including, if relevant, the data controller, the data custodian and the ethics committee.
4. Requests for data sharing must be made on specific grounds with a justification based on public health interest, including:
 - To corroborate the study results if there is evidence of conflicting results with different studies addressing the same research question, or in case of suspected methodological issues which might impact on the study outcome (such as the statistical analysis performed);
 - To perform additional research based on the data, such as a patient-based meta-analysis, sub-group analyses, accounting for confounding factors, use of alternative statistical methods, or testing of new hypotheses with public health impact;
 - In the context of an audit by a national competent authority.
5. The decision to share study data lies with the study team or a delegated appropriate committee. The public health objective of the request and the scientific quality of the protocol should be considered for the decision.
6. Analyses performed with shared data must follow the provisions of the ADVANCE Code of Conduct, including making available the request for data sharing and the response provided. The data requester may be asked for fair compensation for dataset preparation and analysis.


Additional reading:[12],[31]

4.7.10. Research contract

Definition

Research contract means a written agreement between two or more parties involved in a research project, intended to be enforceable by law.

The research contract may have different objectives. It will set the terms and conditions of the collaboration between the parties for the conduct of the study, which can differ for each study. The research contract may set out the conditions under which, for example:


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- Funding is provided by a party or parties to the other party or parties for a research project;
- Part of the research project is sub-contracted by one party to another one;
- Different parties agree to enter into a collaboration for a same project;
- The provider of primary data will give access to the data and allow their secondary use for a research project.

Recommendations


47. A research contract must never lead investigators or other entities, directly or indirectly, to violate the principles of the Helsinki Declaration for medical research [27], or act against applicable legal or regulatory obligations.
48. Key elements of any research contract are clarity and transparency: all relevant aspects must be covered in a way that is understandable by all the parties concerned.
49. In cases where several parties interact in the study, a unique multipartite contract is preferred to support transparency and clarity on roles and responsibilities. In cases where several bipartite contracts need to be established for the same study, the terms of agreement should be communicated to the management entity of the study.
50. Research contracts should indicate that the conduct of the study will follow the recommendations of the ADVANCE Code of Conduct and describe the following elements:
 - scientific rationale, main objectives and brief description of the research to be carried out;
 - the work to be undertaken and the tasks covered by the contract (with deliverables and milestones as appropriate and contingency plans if timelines cannot be met), as well as the roles and responsibilities of the different parties for their implementation;
 - rights and obligations of each of the concerned entities
 - communication plan for the scheduled progress and final reports;
 - publication policy and authorship;
 - intellectual property rights on the protocol and results;
 - process for disclosure, update and management of potential conflicts of interests;
 - transparency measures: which information will be made public, and how; provision regarding registration of the study and publication of the protocol;
 - archiving of data, rights of data ownerships and access to data;
 - storage and availability of analytical dataset and statistical programmes for regulatory audit and inspection;
 - if relevant, provisions for meeting pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable;
 - the financial contributions/payment terms of the contract.

Additional reading:[2],[3],[12],[16],[32]


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4.7.11. References

- [1] KNAW (Royal Netherlands Academy of Arts and Sciences). Responsible research data management and the prevention of scientific misconduct, p. 73, https://www.knaw.nl/nl/actueel/publicaties/responsible-research-data-management-and-the-prevention-of-scientific-misconduct?set_language=en; 2013 [accessed 03.08.16].
- [2] IEA. Good Epidemiological Practice (GEP), <http://ieaweb.org/good-epidemiological-practice-gep/>; 2007 [accessed 03.08.16].
- [3] ISPE. Guidelines for good pharmacoepidemiology practice (GPP), http://www.pharmacoepi.org/resources/guidelines_08027.cfm; 2015 [accessed 03.08.16].
- [4] All European Academies (ALLEA). The European Code of Conduct for Research Integrity http://www.esf.org/fileadmin/Public_documents/Publications/Code_Conduct_ResearchIntegrity.pdf; 2011 [accessed 03.08.16].
- [5] European Commission. The European Charter for Researchers. <http://ec.europa.eu/euraxess/index.cfm/rights/europeanCharter>; [accessed 03.08.16].
- [6] IARC. Code of Good Scientific Practice, http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk4/IARC_Code.pdf; 2008 [accessed 03.08.16].
- [7] Montreal Statement on Research Integrity in Cross-Boundary Research Collaborations, <http://www.researchintegrity.org/Statements/Montreal%20Statement%20English.pdf>; 2013 [accessed 03.08.16].
- [8] Singapore Statement on Research Integrity, <http://www.singaporestatement.org/>; 2010 [accessed 03.08.16].
- [9] Thompson A, Komparic A, Smith MJ. Ethical considerations in post-market-approval monitoring and regulation of vaccines. *Vaccines* 2014;32:7171-4.
- [10] VSNU (Association of Universities in the Netherlands). The Netherlands Code of Conduct for Scientific Practice, http://www.vsnul.nl/files/documenten/Domeinen/Onderzoek/The_Netherlands_Code_of_Conduct_for_Scientific_Practice_2012.pdf; 2012 [accessed 03.08.16].
- [11] Department of Health UK. Research Governance Framework for Health and Social Care, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/139565/dh_4122427.pdf; 2005 [accessed 03.08.16].
- [12] ENCePP. ENCePP Code of Conduct, http://www.encepp.eu/code_of_conduct/index.shtml; 2014 [accessed 03.08.16].
- [13] EFPIA. EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Health Care Professionals, <http://transparency.efpia.eu/uploads/Modules/Documents/efpia-hcp-code---2013-consolidated-final-2.pdf>; 2013 [accessed 03.08.16].


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- [14] Federation of the medical scientific associations. Code of conduct for health research, https://www.federa.org/sites/default/files/bijlagen/coreon/code_of_conduct_for_medical_research_1.pdf; [accessed 03.08.16].
- [15] Hemmati M. Multi-stakeholder Processes for Governance and Sustainability: Beyond Deadlock and Conflict. Earthscan Publications Ltd, London, http://www.wageningenportals.nl/sites/default/files/resource/multi_stakeholder_processes_for_governance_and_sustainability_hemmati_2002.pdf; 2002 [accessed 03.08.16].
- [16] EMA. Guideline of good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies (Rev 2), http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c; 2016 [accessed 03.08.16].
- [17] ADELf. Recommendations for professional standards and good epidemiological practices, <http://adelf.isped.u-bordeaux2.fr/LinkClick.aspx?fileticket=AmROQnGh14o%3D&tabid=534>; 2007 [accessed 03.08.16].
- [18] Nefarma (Dutch association of innovative industry). Code of conduct on Transparency of Financial Relations, <http://www.nefarma.nl/cms/streambin.aspx?requestid=F21F264A-A1BF-4D0E-ADB3-46569B1DC2FA>; 2015 [accessed 03.08.16].
- [19] The Royal Netherlands Academy of Arts and Sciences (KNAW) and the Royal Dutch Medical Association (KNMG). Code for the prevention of improper influence due to conflicts of interest, https://www.knaw.nl/shared/resources/actueel/publicaties/pdf/code_digitale_2012_eng_def_interactief3.pdf; 2012 [accessed 03.08.16].
- [20] EMA. Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies, http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf; 2012 [accessed 03.08.16].
- [21] ENCePP. ENCePP Checklist for study protocols, http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml; 2016 [accessed 03.08.16].
- [22] CONSORT Group, CONSORT: Consolidated Standards of Reporting Trials, <http://www.consort-statement.org/>; 2010 [accessed 03.08.16].
- [23] EMA. Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf; 2013 [accessed 03.08.16].
- [24] STROBE Initiative, Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies, <http://www.strobe-statement.org/index.php?id=available-checklists>; 2007 [accessed 03.08.16].
- [25] EMA. Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases,

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http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/12/WC500157839.pdf; 2013 [accessed 03.08.16].

- [26] ICJME. Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/urm_main.html; 2015 [accessed 03.08.16].
- [27] WMA. Revised WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, <http://www.wma.net/en/30publications/10policies/b3/index.html>; 2013 [accessed 03.08.16].
- [28] European Data Protection Supervisor. Glossary. <https://secure.edps.europa.eu/EDPSWEB/edps/EDPS/Dataprotection/Glossary> [accessed 03.08.16].
- [29] Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf [accessed 03.08.16].
- [30] Good Epidemiological Practice (GEP). IEA Guidelines for proper conduct in epidemiological research, <http://ieaweb.org/good-epidemiological-practice-gep/>; 2007 [accessed 03.08.16].
- [31] ENCePP. ENCePP Code of Conduct – Implementation Guidance for Sharing of ENCePP Study Data, http://www.encepp.eu/code_of_conduct/documents/Annex4_SharingData.pdf; 2011 [accessed 03.08.16].
- [32] AGENS, DGSPM and DGEpi. GPS – Good Practice in Secondary Data Analysis, http://dgepi.de/fileadmin/pdf/leitlinien/gps-version2-final_ENG.pdf; 2008 [accessed 03.08.16].

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4.8. Appendix 2. The Study Team

4.8.1. Definition

The study team is a group of individuals - not organisations - playing the central role in the scientific and operational decision-making regarding the implementation of a specific study. Each study team member has adequate education, training, experience and expertise to fulfil a specific role in the study implementation. The study team contributes collectively to the design, feasibility assessment, execution, interpretation and reporting of the study, ensuring compliance with the principles of scientific integrity and transparency throughout the study lifecycle (see recommendation 2).

4.8.2. Study team composition

The main criterion for membership is a documented scientific expertise relevant for the research question (see recommendations 1-3). As such, membership should not be based solely on affiliation with a specific partner in the project or with any specific type of organisation. However, study team members should have sufficient autonomy within their respective organisation (see recommendation 5) and the organisation they belong to should commit enough time and resources to ensure that study team members can fulfil their role in the study.

When relevant, it is useful to define a *core study team*, which would include the principal investigator (PI) as well as persons with key functions (such as statistician, disease epidemiologist, pharmacoepidemiologist or clinician) and a *team of support functions* (such as project manager, statistical programmer, data manager or scientific writer). In this case, the decision-making will fall within the responsibility of the core study team.

Special consideration should be given to assess whether database owners, custodians or data controllers should be members of the study team, according the principles and recommendations of the ADVANCE Code of Conduct; if this is the case, it should be clarified whether they participate in the core or support team and what their specific role(s) will be in the specific study.

If access to study data is restricted to some study team members, this restriction should be justified and documented with a clear description of who will have access to which data.

The governance model for the collaboration or partnership under which a study is conducted should include a clear description of the nomination process for the PI and study team members.


4.8.3. Role

The role of the study team is to design and complete the study according to the study protocol, and this includes the entire decision making process applied within this framework.

4.8.4. Responsibilities

Responsibilities of the study team include:


- Ensuring compliance with the ADVANCE Code of Conduct and other relevant guidelines (see recommendation 3). A principle-based approach is recommended for all decisions and refreshing the study team members on principles of ethics and scientific integrity should be considered.

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- Ensuring adequate transparency on the development and implementation of the study, including study team membership, Declarations of Interest of study team members, protocol contents, result interpretation, study report, publications, including comments received on the various study documents (see recommendations 7-13 and 15)
- Organising peer-review with external experts or an external advisory board for important study documents such as the study protocol and study report (see recommendation 6)
- Delivering the protocol and the study report according to the recommendations set out in the Code of Conduct
- Ensuring posting of the study protocol and results (see recommendation 7 and 11)
- Publishing the study results (see recommendation 33), including the organisation of a transparent review of comments received, while the final decision-making remains with the PI and the study team.
- Rapidly informing regulatory and public health authorities of the results of the study if needed (recommendation 35).
- Reviewing requests for study data sharing and organising data sharing as applicable (see recommendation 44).


4.8.5. Authorship

Authors of the study report must be from the study team. Authors of the publications should be the study team members who are fulfilling the ICMJE criteria (see recommendation 32).

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5. Module 2. Governance models

This module has been submitted separately as Deliverable 1.10, which will be reviewed by WP7 for its implementability and feasibility. It will be integrated in the good practice guidance as part of the ADVANCE blueprint following its finalisation.

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6. Module 3. Quality management

6.1. Abstract

Key aspects identified to be addressed by a future framework for vaccine benefit-risk monitoring included “Quality assurance and quality control”. Quality of research requires a set of activities aimed to direct, control and coordinate quality – i.e. Quality Management (QM). QM is a continuum of activities that aim to prevent, detect, correct, control errors. An overview of elements of essential quality management activities was deemed useful to promote quality and facilitate rapid implementation of research. A review was conducted for commonly referenced good practice guidelines and regulatory guidance applicable to observational research in the area of quality management. The current guidance provides limited description of the aspects of quality assurance through written procedures and governance around them, as well as the organisational conditions and the active planning of quality control through monitoring, (self) audit and their resulting actions that ensure a continuous improvement cycle. A baseline inventory of the current status of implementation of quality management among the ADVANCE stakeholders likewise showed a gap for the same type of elements of quality management. The Quality Module embedded in this deliverable provides an overview of the elements of essential quality management activities. This overview will serve for the evaluation of the implementation of good quality practices in the proof-of-concept studies. The final result will be an implementable guidance on quality management for observational research endorsed by all stakeholders in the ADVANCE Blue Print.

6.2. Concept and definitions


For the purpose of this document the below definitions are applied. Where available they have been taking from the European context and/or the area of observational research given the scope ADVANCE.

6.2.1. Quality in observational research

There are many definitions of quality available. The International Organisation for Standardization (ISO) defines quality as “*the degree to which a set of inherent characteristics of an object fulfils requirements*” [1]. Quality includes, but is generally not limited to, compliance where it pertains to meeting requirements by law.

Specifically to the field of drug research, the Clinical Trials Transformation Initiative (CTTI) has characterised ‘quality’ of clinical trials as, “*the ability to effectively answer the intended question about the benefits and risks of a medical product or procedure, while assuring protection of human subjects*”. [2] In its core, the same definition of ‘quality’ can be applied to observational research, with the understanding that:

- The benefit/risk question intended to be answered by observational studies and the decision making based on them may differ from those of clinical trials. This difference is most apparent in comparison to pivotal trial(s) used for the decision making on product licensure, which is currently only in exceptional cases based on observational studies. In such a situation, such evidence will inevitably lead to a decision. However, in a post-marketing context this difference is generally less pronounced. Comparable to clinical trial results, the evidence from observational studies will inform decision-making at the level of clinical practice and can

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influence the extent and targeting of use of interventions by driving reimbursement, recommendation and prescribing practices. And while unlikely and generally would be inappropriate to base on only a single study, on a regulatory level, observational studies can lead or contribute to decisions on restricting or expanding the approved indication and possibly licensure withdrawal with potential high societal impact.

- Aspects of human protection differs between observational studies and clinical trials. In observational studies, by definition the intervention (or diagnostic) is independent of the protocol. As such, the risk for subjects is generally considered to be lower in observational studies, given the nature of the risk (psychological vs physical or privacy vs health related risk) and the level of the risk (societal vs individual).

These aspects do not necessarily require a different definition of quality for observational studies nor materially change how quality is achieved – but what can be considered as “sufficient” ability to effectively answer the B/R question may be proportionally driven by the expected decision making based on them. In this context, studies undertaken by market authorisation holders (MAHs) and regulators are subject to specific requirements by law and regulation.

Quality Management as per the ENCePP Guide on Methodological Standards in Pharmacoepidemiology [3] *implies and consists in activities of quality planning, quality assurance, quality control and quality improvement. **Quality planning** is defined as a set of activities whose purpose is to define quality system policies, objectives and requirements, and to explain how these policies will be applied and achieved, and how these requirements will be met. **Quality assurance (QA)** defines the standards to be followed in order to meet the quality requirements for a product or service, whereas **Quality control (QC)** ensures that these defined standards are followed at every step. Although QA and QC are closely related concepts, both are aspects of quality management and both form an integral part of the quality management plan. However they are fundamentally different in their focus: QC is used to verify the quality of the output while QA is the process of managing for quality.*


QM is a continuum of activities that applies to the design, conduct (incl. data recording) and reporting of studies. The activities include to prevent, detect, correct, or control common types of errors likely to occur in research: design-related, procedural, recording (random or fraudulent) and analytical errors. Sustainable QM is a joint responsibility by all of the parties involved and demands a proportionate approach to resources and planning. The system can be flexible and taking a more risk based approach - adapted to the likelihood of occurrence of a hazardous event and the consequence of that event to subjects, quality of data and results and subsequent consequences for the anticipated decision-making.

6.2.2. Other

Observational study (as per the Good pharmacovigilance practice Module VIII, Rev. 2)[4]:

A study is non-interventional if the following requirements are cumulatively fulfilled:

- *the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;*
- *the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and*

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- *no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.*

The terms observational study and non-interventional are here considered synonymous in line with GVP.

Clinical trial (as per the European Clinical Trial Directive) [5]:

Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

The terms clinical trial and clinical study are synonymous.


6.3. Quality management in the context of ADVANCE

Effective collaboration between stakeholders and governance for the conduct of studies are among the main objectives of ADVANCE. In this context, Work Package 1 will develop a good practice guidance including core values to be integrated in this framework, models for interactions, principles of governance between public private stakeholders and quality management as components of a sustainable, transparent and high quality organisation of vaccine studies and trust into vaccination programmes.

The starting point of the work of WP1 has been a needs assessment among the stakeholders. From the variety of needs and requirements expressed by stakeholders (sometimes with different wording or in different contexts) (see ADVANCE Deliverable 1.5). Key aspects to be addressed by a future framework for vaccine benefit-risk monitoring have been identified, including “Quality assurance and quality control”.

Among the identified needs, “high data quality” was a prerequisite expressed by all stakeholders in that studies should be of a sufficiently high quality as to provide the public, health care professionals, regulators and other stakeholders with confidence in the results. This need was further described as a requirement for confidence in terms of data quality to be agreed between stakeholders for mutual acceptance. This included various aspects: the completeness, accuracy and validity of the source data and coding systems used for particular types of studies, the validity of the steps of data integration, analysis and interpretation, the way results are presented and the confidence that results contribute to the evidence base. Quality therefore was not considered as limited to the data but also to the complete process of the research. Standardised data quality control procedures were highlighted as an important aspect of data quality. While quality management is often applied to observational studies, it was agreed that these measures should be applied, recorded and reported for all studies. The Good Practice Guidance to be developed by WP1 therefore includes a section on requirements for quality control and quality assurance which are endorsed by the stakeholders.

Guidelines with recommendations on the planning and conduct of epidemiological studies are available. Most of them were developed by learned societies and professional associations at national and international levels based on a large amount of experience and expertise. In 2012, the new pharmacovigilance legislation that came into force in Europe, which provided a regulatory framework for the post-authorisation monitoring of medicinal products, including vaccines, translated into a series of Modules of Good Pharmacovigilance Practices (GVP) issued by the European Medicines Agency

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(EMA). The GVP has formalised several quality management aspects around the conduct of observational studies.

However, GVP applies to marketing-authorisation holders, the EMA and medicines regulatory authorities in EU Member States. The GVP holds requirements for a range of activities of these organizations, including observational and clinical trials. Observational studies that are initiated, managed or financed by MAH must adhere to the GVP. The GVP is not applicable outside this stakeholder environment and is thus relatively unknown by many researchers conducting vaccine benefit risk monitoring. Increased awareness among public organisations is needed on these regulatory requirements to ensure compliance and closing remaining gaps in elements of quality management when performing a study within a public-private partnership.

6.4. Objectives

Given the outcome of the needs assessment as described in section 6.3, the objectives of the WP1 Working Group 2 on Quality were to:

- Review existing guidelines on elements of Quality Management for Observational Research
- Assess the current status of quality control and assurance implementation among stakeholders through the conduct of a consortium survey
- Assess the need of, and accordingly, establish a consolidated Good Practice Guidance on Quality Management
- Test and evaluate the implementation of good practices in the proof-of-concept studies and assess risks of identified gaps
- Integrate guidance on quality management of observational research endorsed by all stakeholders in the final ADVANCE Blue Print.

6.5. Methods


6.5.1. Review of existing guidelines on elements of quality management

The purpose of the review was to:

- Give an overview of the elements of quality management described in the commonly referenced good practice guidelines and regulatory guidance applicable to observational research.
- Identify indicators of implementation of quality management for use in the survey to assess their current implementation status.

The review focused on the most recognized and referenced good practice guidelines and the EMA regulatory guidance applicable and relevant to the conduct of observational studies as identified by the WP1 Quality working group members and focusing on the European (regulatory) context. These guidelines included:²

² See references in Module 1, Code of Conduct.

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- International Society for Pharmacoepidemiology- Guidelines for Good Pharmaco-epidemiological Practice (GPP)[6]
- International Epidemiological Association- Good Epidemiological guidelines (GEP)[7]
- EMA Good pharmacovigilance practices (GVP):
 - o Module I Pharmacovigilance systems and their quality systems [8]
 - o Module VIII Post-authorisation safety studies³ [4]
- International ethical guidelines for epidemiological studies [9].

In addition to the initial reviewed guidelines, the following supporting materials were consulted for this purpose:

- ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Chapter 6: Quality management. [10]
- Guidelines for good database selection and use in pharmacoepidemiology research. ([11]
- The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. [12]
- Eudralex 11: Computerized systems [13]; ISO Standards [14]
- International Conference of Harmonization Guideline for Good Clinical Practice (GCP) E6(R1) [15]
- Quality assurance and quality control in longitudinal studies [16].

6.5.2. Consortium survey on current status of quality management implementation


The objective of the survey was to obtain a baseline inventory of the current status of implementation of elements of quality control and assurance among the ADVANCE stakeholders, including those that are required by the GVP.

To achieve the survey's objective and for practical reasons, the survey was not intended to be exhaustive on all elements of quality management. The review of the guidelines and guidance (as described above) served as the basis for selection of criteria to be included in the consortium survey. A selection was made of criteria which were considered to reflect implementation of quality assurance and control activities, including those required by the regulatory guidance. Activities of quality assurance and control which were found to be lacking or limited addressed in the guidelines were added to the survey. Quality management activities which were mentioned in more than one guideline or guidance, but using different terminology, were adapted for the purpose of the survey.

The final survey consisted of 48 quality criteria across 6 categories, listed below with some examples of the elements covered in the criteria (for the full list see Annex 2):

- Study – protocol, report and responsibility for execution
- Human protection – ethics, informed consent, privacy protection
- Expertise – qualification of the personnel, training
- Data – analysis plan, programming
- Security and storage – access, archiving facilities

3 For the survey and the review version 19 April 2013 EMA/813938/2011 Rev 1* was used

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- Quality Management – written procedures

Five questions were asked on each of these:

1. Is this considered important?
2. Is this currently, in some form, implemented in your organisation?
3. If implemented, is that done through a written procedure (Standard operating procedures or work instructions)?
4. If a written procedure exists, is there a procedure for adherence check in place?
5. If not implemented (question 2), is it feasible to implement it?

The survey was sent to 27 ADVANCE partners and 16 associate partners. The survey results were analysed across and by stakeholder group – regulatory, EFPIA, academia, small medium enterprises and public health institutes.

The results of the survey were discussed at the General Assembly Meeting (Barcelona, 20 April 2015) and feedback and clarifications were additionally obtained from the stakeholders.

6.5.3. Quality management in the Proof-of-Concept studies

The execution of the POC studies will be evaluated against the elements of the Good Practice Guidance Module for Quality Management as presented herein

6.5.4. Consensus building

The collective results and findings, including the POC evaluation on quality, will be evaluated among the stakeholders. This will involve a risk assessment of remaining gaps to support prioritization of quality management activities [17]. Depending on this, the final consensus will be reflected in the final Blueprint. Considerations will also be given to templates, beyond the study protocol.


6.6. Findings

6.6.1. Review of the existing guidelines

Several observations were made from the review. The guidelines differ according to the affiliation of the authors (scientific vs regulatory), topic of the observational research (general (disease) epidemiology vs pharmaco-epidemiology), type of observational research addressed (primary data collection vs secondary database studies) and scope of their content (study conduct vs ethics). Hence, it was not expected that each guideline would cover all elements of quality management.

In regards to their content, the **Good Epidemiological guidelines (GEP)** [7] focus on rules for good research behaviour which is described across four topics: working with personal data, data documentation, publication and exercise of judgment. There is also a short section on scientific misconduct. Considerations for the study protocol are described in-depth. However, it is lacking aspects of quality management around data analysis, measures of quality control and application of procedures in general or procedures around common study related activities such as document management.

The **Good Pharmacoepidemiological Practice (GPP)** [6] is similar to the GEP in that it aims to provide guidance on the process of study conduct. It includes more extensive considerations on data management and analysis, likely driven by the commonly used methods and data sources in the field

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of pharmacoepidemiology, such as secondary databases. Compared to the GEP, it is more complete in that it addresses all steps in the research process. The GPP also gives attention to the conditions needed for proper study execution (i.e. resources, facilities, contract). The use of written procedures is primarily addressed in the context of data analysis. While inspection as measure of quality control is mentioned, the use of self-audit mechanisms and continuous improvement cycles is not explicitly addressed.

Table 1 provides a qualitative comparison of the elements of study conduct addressed in the GEP and GPP guidelines, both which are more generic to observational study conduct.

Next to these two more generic guidelines, the **Good pharmacovigilance practices (GVP)**[4],[8] focus on elements of study conduct relevant to the regulatory framework. Also here, the study protocol is positioned as the cornerstone of any study and provides explicit guidance on its conduct to be followed by MAHs for post-authorisation safety studies. It also places emphasis on quality control measures through audit and inspection. The **International Ethical Guidelines for Epidemiological Studies** [9] focus on the ethical considerations.


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Table 1: Qualitative assessment of the level of guidance provided in GEP and GPP guidelines* across elements of study conduct**


Elements of study conduct	GEP [7]	GPP [6]
Study protocol	++	++++
Resource management	-	++
Ethics and human (data) protection	++++	+++
Procedures	--	-
Data management	-	+
Document management and archiving	--	+/- (list of documents required for archiving)
Analysis and reporting	+/- (primarily reporting)	++
Security	+/-	+
Monitoring, audit and inspection	---	+/-
Contracting	-	+

* The International Ethical Guidelines for Epidemiological Studies and GVP were not included as their scope is more specific.

** The notation of plus (+) and minus (-) provide an indication of the extent to which the elements of study conduct have been described: ranging on a continuous scale from extensively described (++++) to not or very limitedly described (---). The ratings should be viewed relative to each other and qualitatively.

Across guidelines, overlap on the topics covered is particularly seen for the elements of study protocol writing and human (data) protection, the latter having its basis in the legislation and the Declaration of Helsinki. Where overlap exists, the guidelines varied in level of details of their description. As was particularly the case for the study protocol, the GPP and GEP guidelines provide quite extensive details of the characteristics and content of the protocol. However, limited attention is given to the actual process of creation, review and amendment of the study protocol, i.e. the quality assurance measures that would support fulfilment of the specified requirements. This was generally also the case for all other steps of the research process. Also, most topics were directly related to study conduct and less elaborated on the organisational aspects (i.e. assigned responsibility) of quality management by the executing organisations and the conditions needed for proper study conduct. No apparent distinction of importance or prioritisation for adherence was provided for the activities mentioned, except perhaps what may be inferred from the difference in level of detail.

Comparing the GEP and the GPP, the GPP provides the more complete guidance on the activities that can help ensure the quality of the research. However, for this guideline as well as for the GEP, there is limited description of the aspects of quality assurance through written procedures and governance around them, as well as the organisational conditions and the active planning of monitoring activities (quality control), and auditing (quality assurance) and their resulting actions that provides a continuous

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improvement cycle. These aspects are generally considered an essential part of quality management which can ensure a more structural approach to quality.

6.6.2. Survey results on implementation status of Quality Management

The survey resulted in 17 responses. Figure 1 shows the response rate across the ADVANCE stakeholder groups. Several regulatory stakeholders indicated their organisations generally did not perform studies making it difficult to complete the survey. Several participants indicated that they had to consult further internally to verify if the listed elements were implemented, but this step did not always provide a conclusive answer. Not all of the stakeholders were familiar with the applied terminology in the survey leaving some room for interpretation which may have influenced the results.

Figure 1: Response rate for the survey on implementation status of quality management

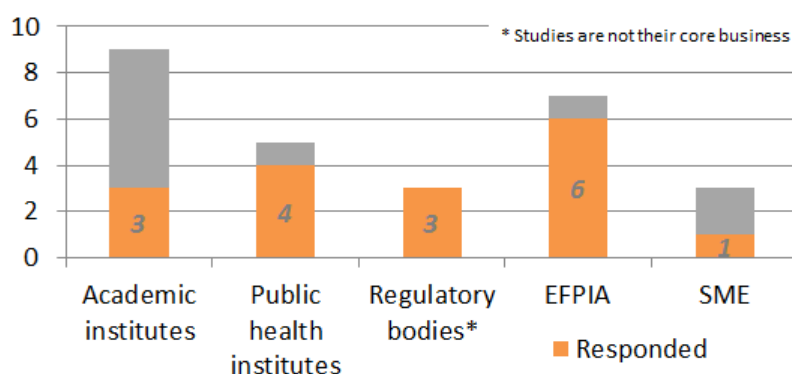


Figure 2 shows that written procedures and adherence checks are more frequently available among participants belonging to the EFPIA group. This can be expected given that the EFPIA requirements are already built around GCP standards. However, for the other stakeholders, while the respondents confirmed that the quality activity was implemented, the percentages went further down as regards written procedure and adherence checks. The overall willingness to implement items that are not currently in place appears high.


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Figure 2: Importance and current status of implementation – all criteria

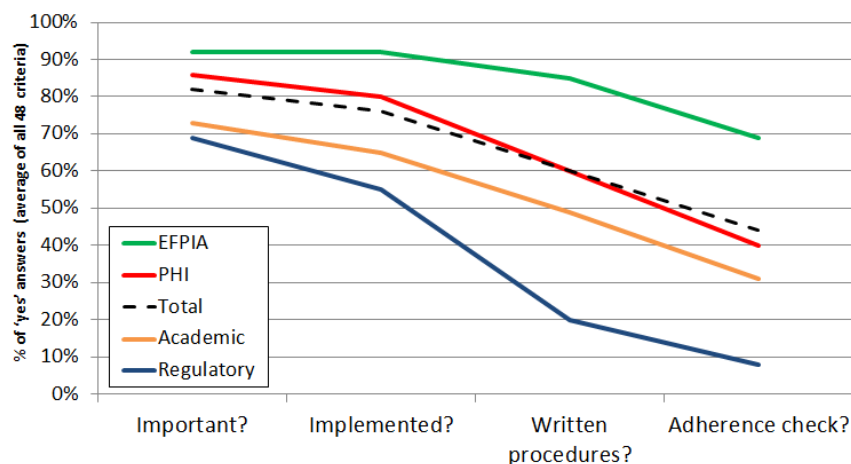



Figure 3: Survey responses on the different criteria by all stakeholders



Figure 3 shows the responses by stakeholder for the criteria per category (see Annex 3 for the list of criteria). In the area of quality management, gaps exist. Like the review of the guidelines, the stakeholder survey also showed a gap in the availability or written procedures beyond the study protocol and relevant to the execution of the study. Although this could not be verified, the survey results may suggest that the absence of implementation of these elements may be due to the fact that the guidelines and specifically the GEP guideline do not highlight these. Developing a quality system requires significant resources, which may represent a constraint, as highlighted during the General Assembly Meeting.


Items with a high rate of non-implementation were found across all 6 themes, except for the theme “security and data integrity”. Overall, the highest non-implementation rate was found in the “quality management process” part.

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Several of the criteria listed in the GPP were also included in the survey, but not implemented. In part this may be explained by the fact that the consortium includes representatives from organisations who normally do not conduct pharmaco-epidemiological research.

Among the stakeholders, several indicated that they are not involved in pharmaco-epidemiological research, research that falls under GVP, or do not conduct research for/with marketing authorisation holders. Hence they cannot be expected to maintain activities of quality management on an ongoing basis – the available resources would not be sufficient. Also, the sites do not expect to be able to change the level of quality management overnight to meet newly introduced standards. Prioritisation would be needed to make such implementation feasible. A practical list of essential elements of such quality management activities could help to implement such activities. It would also help prioritise activities of quality management which may be required in limited resource settings.

More details on the results from the survey are included in Annex 3.

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6.7. Good Practice Guidance on Quality management

This guidance is preliminary and is due to undergo further review by the ADVANCE consortium.

6.7.1. Introduction and scope

The Good Practice Guidance on Quality Management provides an overview of essential elements of quality management activities in relation observational study management. Activities of QM are described in relation to the following areas:


1. Study protocol
2. Resource management
3. Ethics and Human (data) protection
4. Procedures
5. Data management
6. Document management and archiving
7. Analysis and reporting
8. Security
9. Monitoring, audit and inspection
10. Contracting

While some practices listed here are also formalised by law or regulatory guidance, an exhaustive overview of the requirements itself are not in the scope of this module, which only covers the QM practices that support their achievement. This is with the exception of the list of requirements from the GVP – which have been included as Annex 4 to this Module. Applicable (local) regulatory requirements and legislation should always be verified before initiating an observational study to ensure that compliance with these requirements is met. Advice should be sought from local regulatory agencies and ethics committees as needed.

6.7.2. Study protocol

The overall quality of an observational research project depends on how well both the design and execution phases of the project have been accomplished. A major cornerstone of the quality of any study is the availability of a written study protocol before undertaking a study. The written protocol translates study design into execution, therefore playing a pivotal role in determining the quality of the total research effort. The study protocol can contribute to improved scientific integrity and documentation and supports the efficiency and communications between the members of the study team. The feasibility of its execution should where possible be verified through feasibility assessment conducted prior to or as part of the protocol development and reported in the protocol.

Important activities of QM relevant for the protocol development are the standardization of its creation (i.e. templates following existing guidelines) as well as the process of review, approval and revision and documentation thereof. Review by external IEC/IRB and regulatory authorities also helps ensure that the research is evaluated by a party that is independent and that complies with the requirements

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established by national and local laws and regulations. After the study has been initiated, monitoring of the activities should be performed to ensure that protocol compliance is maintained (see 6.8.9 Monitoring, audit and inspection).

Key elements for implementation:

- i. A written final study protocol is established before study start
- ii. Feasibility assessments are conducted as part of protocol development and reported in the protocol.
- iii. A template is used for protocol development, compliant with applicable guidances
- iv. Written documentation of relevant expert review of protocol is available
- v. Procedure(s) are in place which specify protocol (amendment) preparation, review, required approvals and change management. See also section 4. Procedures.
- vi. Required approval of regulatory agencies and/or relevant Ethics Committees (EC) is obtained prior to study starts and implementation of any amendment
- vii. All other study documentation is in compliance with and reference the effective version of the protocol.

6.7.3. Resources

Study members tasked with the development and/or execution of the study protocol have a direct impact on the quality of a study. QM activities should support to ensuring that study team members have the appropriate expertise (i.e. qualified by education and experience) and permitted to perform these tasks by law, and that no restrictions or disqualifications apply. Defining which competencies are required of the study team members, identifying these competencies during study team member selection and/or training them to obtain the required competencies are essential activities for achieving quality. Selecting competent study team members ensures that members are aware of the aspects of their activities that present a risk to the availability and/or robustness of study results. .


Beyond the qualifications of the study members by education and documented experience, study team members should be informed (i.e. through training, review) uniformly about the protocol, and trained on requirements, policies, and procedures to ensure appropriate, and consistent, protocol implementation.

Similar to assigning qualified personnel, it is likewise important to assign sufficient and reasonable capacity to complete each of the study tasks as outlined in the protocol and related procedures. QM activities aimed at ensuring sufficient qualified resources thus also include assessments of the required resources in terms of capacity.

Potential conflicts of interest, including financial, that interfere with the conduct of the study or interpretation of results should be verified. (see also Module 1 Code of Conduct)

Similar principles apply to third parties such as members of assigned committees (i.e. adjudication committees).

Key elements for implementation:

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- i. Responsibilities of each study team member are defined
- ii. All study personnel is determined to be qualified and permitted by law to perform their tasks.
- iii. Declaration of interest statements are obtained
- iv. Commitment is given for resources allocation and based on a documented assessment of the required resources (capacity and competence)
- v. Study specific training requirements are defined
- vi. Study personnel is trained on the latest versions of relevant study documentation before performing their duties
- vii. Training records (dated, named) and qualification (i.e. CV) are collected and updated during the study.

For the topic of declaration of interest see also Module 1. Code of Conduct, Appendix 1 The ADVANCE Code of Conduct, Section 4.7.4. Conflict of interest. And for the topic of study team see Module 1. Code of Conduct, Appendix 2 The Study Team of the ADVANCE of this document.

6.7.4. Ethics and Human (data) protection

The definition of quality in this context also includes assuring that protection of human subjects is ensured and compliant with applicable legislation on data protection and ethics. Protocol and informed consent authors have a responsibility to identify and describe the foreseeable risks and benefit(s) for the individual subject and/or society. For risks, this allows measures for their mitigation can be identified and implemented. Where required, informed consent should provide sufficient information so that a participant can make an informed decision about whether or not to enrol in a study, or to continue participation, based on an understanding of the risks and benefits of the research. In line with the definition of observational research, the informed consent process should be such that participation is independent of the intervention of interest. Whenever possible in situations where information is obtained directly from human subjects or health care professionals, informed consent is preferably obtained after the intervention of interest has already occurred as part of routine care. .


Ethical and, where applicable, regulatory review of the study protocol and informed consent forms provides external verification that protection of human subjects is sufficient and that legal and regulatory requirements in this respect are met. Privacy of subjects can be protected by organizational measures to prevent unauthorized access or use of data or keeping personally identifiable information separate from the research, but also technically by (pseudo-) anonymisation⁴ or by restricting the research data to that directly relevant for the specific purpose. Confidentiality agreements can warrant privacy for study team members that do have access to personal data.

For measures of security to protect human data see section 8. Security

Key elements for implementation:

- i. Documentation that all data is legally obtained, either by

⁴ As defined by the General Data Protection Regulation, pseudonymisation is the separation of data from direct identifiers so that linkage to an identity is not possible without additional information that is held separately - General Data Protection Regulation

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- o Legally effective informed consent, or
- o Legally valid waiver for informed consent approved by an IRB/EC
- ii. Written documentation of Ethics Committee/Institutional Review Board approval of an appropriate level and as well as a description of its composition
- iii. Signed confidentiality agreement of involved researchers
- iv. Technical and organization measures to protect personal identifiable data are in place (See also section 8. Security)
- v. Only personal data relevant to the study is collected.

6.7.5. Procedures


Procedures are detailed written instructions to achieve uniformity of the performance of a specific function/task. Procedures help maximize operational efficiency and satisfy compliance requirements by distilling those requirements into a format that can be used by staff members in the working environment. Procedures can be standard operating procedures (SOPs) – for common applied processes - or study specific.

Written operating procedures themselves should be governed by a defined procedure on preparation, control, distribution, review, revision and retrieval. Procedures must be periodically reviewed, updated and re-approved as required over their life cycle. Only relevant procedures in their effective version must be available at points of use. All staff applying procedures must have documented training on those procedures before applying the process described in it.

In addition to procedures which describes the actual process, a quality manual preferably defines the quality at the organizational level: the quality policy of an organization, the organizational commitment, the responsible functions for quality, managerial oversight and escalation path in case of issues, and a list of all effective quality related documents (i.e. policies, risk management plans, SOPs, working instructions, forms, templates, logs).

Key elements for implementation:

- i. A list of key processes and systems is available together with their written standard operating procedures.
 - o At minimum standard operating procedures are advised for:
 - Protocol (amendment) preparation, review, required approvals and change management
 - General processes for review, approval and versioning of study specific documents
 - Common steps in the data collection, transfer and processing.
 - Statistical analysis plan and mock tables (amendment) preparation, review, required approvals and change management.
 - Report (amendment) preparation, review, required approvals and change management, including external reviewers

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- o Study specific procedures, in support of the protocol, should preferably include:
 - Project Management Plan (resources, study risk assessment and mitigations, escalation, communication, responsibilities, applicable SOPs, training requirements etc)
 - Data Management plan (transfer, processing, software, locations of the data, security, access etc)
 - Document Management plan (list of essential documents⁵, location, retention etc)
 - If applicable, Safety data management plan (collection and reporting of adverse events/reactions, timelines and formats of exchange)
- ii. Procedure(s) are in place which specify preparation, amendment review, required approvals, periodic review and change management of procedural documents.
- iii. Responsible functions/personnel for quality and escalation paths are defined

6.7.6. Data collection, transfer and processing


QM activities around data collection, transfer and processing are primarily aimed to permit the reconstruction of these activities and to ensure 'data integrity'. Data integrity is the accuracy and consistency of stored data, indicated by an absence of any alteration in data between two updates of a data record. Collection of accurate data is only the first step to of data integrity. It is equally important that errors are not introduced in the transferring data between sources (from paper to electronic, or between databases) and in the processing thereof.

At the design stage, data integrity is imposed when tools for (paper or electronic) data collection and the database are designed and (system) requirements are defined. The software for data collection software and the database must be validated (i.e. verified that it does what it is designed to do in a consistent and reproducible manner), and documentation of appropriate testing procedures must be available.

Data dictionaries provide standardisation (naming, format, values and units) of the data. (Electronic) data capture instruments, applied software and databases should be tested at the start and through ongoing use of error checking and validation routines to ensure proper format and function. Software used for data collection, transfer and processing should preferably be managed based on written processes so ensure appropriate use. Documentation of design specifications, annotated programming and testing results should be kept as part of the study documentation. Specific consideration should be given to pre-defining the handling of missing data.

The raw data collected in a study, forms the basis for any study on which everything else is build. The data should be legible, contemporaneous, original, accurate and attributable to the person entering, generating or altering the data through the use of (system) audit trails. For secondary data, application

⁵ Essential documents are defined by the Good Clinical Practice (GCP) guideline as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. The definition is applied in this context. Differences will however exist between the essential documents which have been defined in GCP for clinical trials versus document that may be considered essential according to the definition in the context of an observational study.

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of these principles may not be under control of the researcher at the point of the original data collection, but rather should be applied for any steps in processing the secondary data to the final data analysis set.

Audit trails are metadata; data which describes the attributes of other data. An audit trail permits the reconstruction of all data transfer and processing activities and should cover the life cycle of the (electronic) records. Performing regular data consistency checks, specifically, when dealing with large datasets, can support to timely identification of errors in completeness and accuracy during the process of data collection, transfer and processing. A standardized process for raising and solving queries will support to document this process. Throughout the process, comprehensive description of the data and contextual information will help (future) researchers to understand, use and find the data. Data storage index should be readable available for audit and inspection purposes.

To mitigate the risk of data loss, regular back-ups of all relevant data and records should be performed and monitored. Equally, procedures should define how data is stored during the study, archived after the study and ultimately disposed after a defined retention period.


Data protection Boards can provide oversight of data management activities to support compliance and data integrity.

Key elements for implementation:

- i. Written standard procedures for common steps in the data collection, transfer and processing.
- ii. Study specific procedures are documented in a Data Management plan
- iii. Standardized data collection (paper or electronic) forms
- iv. Use of validated statistical software for data management (entry, transfer etc)
- v. Availability of data entry guidelines and data dictionaries, specifically for secondary data collection studies
- vi. Documentation of database design, programming specifications, validation and testing results
- vii. A data storage index present for audit and inspection purposes
- viii. Audit trails performed
- ix. Execution of data consistency checks
- x. Annotated programming maintained
- xi. Appointment of a data management board (for primary data collection studies)
- xii. Back-up(s) of electronic data and records in different locations than the primary database

6.7.7. Document management

“Documented information” as defined by ISO means anything written down or captured in some form: written procedures, policies, checklists, forms, or graphics, drawings, flowcharts, diagrams, IT systems. This includes documentation of what needs to be done, when and how (i.e. protocol, written procedures). Additionally, it includes documentation about what has been done to ensure traceability of

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all development, execution, and testing activities in order to reproduce what has been done. Documented information is the main source for auditors to assess the overall quality of operations and end-result.

Use of templates reduces the opportunities for human error and ensures that all required document attributes (page numbering, versions) are included. Documents must be authored, reviewed and approved by authorised and qualified persons according to the type of document and subject matter. Documents must be uniquely identifiable and version-controlled, with traceability on all changes. This ensures that researchers can demonstrate which versions were in use on a particular date, and, essentially, ensure that study team members are using the correct version. Constituent pages must be unambiguously identified such that completeness is evident (e.g. Page 1 of 4).

Once created, documentation must be easy to find and retrieve by use of a defined folder structure and file naming convention, if possible, in a centralized source. During the period of required retention, documents should remain legible. Electronic document management systems can facilitate the document management process and support to demonstrate completeness and authenticity of documentation by tracking actions such as viewing documents, editing files, and deleting or purging documents.

Quality can also be affected by having too many documents or too large documents. This increases the risk that they may not be found and/or may not be read. Careful consideration thus should be made to the level of detail and the types of documents collected and retained – defined in a list of essential documents.

To mitigate the risk of data loss of the documents, regular back-ups of all relevant documentation should be performed and monitored. Equally, procedures should define how documents is stored during the study, archived after the study and ultimately disposed after a defined retention period.


Key elements for implementation:

- i. Standard templates of commonly applicable study related documents (at minimum protocol, statistical analysis plan informed consent, study report) and study specific procedural documents (project management plan, document management plan, data management plan, safety data management plan)
- ii. Written processes for review, approval and versioning of any documents
- iii. Centralised and structured repository for study documentation
- iv. List of essential study documents

6.7.8. Analysis and Reporting

Data analysis must follow methods documented in the study protocol, statistical analysis plan and/or procedures in advance of its execution. The creation of a statistical analysis plan should follow a pre-specified procedure and template. Inclusion of mock tables will facilitate the translation of the protocol to the eventual tables and will shorten the time required for the generation of the final study report.

Programmer specifications should be annotated and specification documents modified as needed, with the goal of recording all decisions and assumptions to determine if the data had been analysed as

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intended. Appropriate programming control procedures should be defined depending on program and executed by independent programmer(s).

The computer software for statistical analysis must be validated (i.e. verified that it does what it is designed to do in a consistent and reproducible manner), and documentation of appropriate testing procedures must be available.

The study reports (progress, interim and final) should follow a pre-defined template, compliant with the format and content as required by law or regulation. Any deviations from the protocol or from the statistical analysis plan must be clearly documented in the report and a reasonable explanation should be provided.

Written procedures should be available that describes the process of review and approval of the study report and the documentation thereof. A draft study report should undergo review by the relevant study team members, required approvers and independent review by experts that did not participate to its writing or directly involved in the study.

Key elements for implementation:

- i. Written procedure for the development of the Statistical Analytical Plan (SAP), including mock tables.
- ii. Standardized compliant template for study reports
- iii. Written process on review and approval process of study reports, including external reviewers
- iv. Documented expert review
- v. Annotated programming performed
- vi. Defined quality control processes for programming.

6.7.9. Security and storage


All study information (data and documents) should be handled and stored so as to ensure that the confidentiality of the records of the study subjects as well as that the data integrity remains protected.

Where study information is kept, by default access of personnel should be restricted unless specifically authorised. Whenever possible, access of persons should be arranged at the following three layers:

- Physical access to premises or specific study or storage locations
- Logical access to the operating system (i.e. system accounts and access to data folders).
- Logical access to the application (i.e. a valid account within the application)

Security logs should be generated at each level to confirm unauthorized access has not taken place. Passwords managed access should require strong passwords.

Storage facilities must be physically secure, fit for purpose and reserved exclusively for their designated purpose. Access must be controlled and restricted as far as possible, to those directly responsible for storage and retrieval operations. Storage locations must have a controlled atmosphere to protect stored items from damage or decay.

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As a general rule, protected health information should never be transmitted over the internet without encryption – and should where possible be devoid of personal identifiers.

A Disaster Recovery Plan can ensure the continuation of vital research processes in the event that a disaster occurs by minimizing downtime, remaining compliant and ensuring data are protected.

Key elements for implementation:

- i. Use of security logs for systems and storage
- ii. Strong passwords are applied
- iii. Encryption is applied when transferring protected health information
- iv. Designated and controlled areas for data storage
- iv. Disaster and Recovery Plan should be available describing back-up solutions and recovery processes

6.7.10. Monitoring, Audit and Inspection

Throughout the study, the study team should maintain track of issues, document and assess their impact, and provide mitigation as required.


The purpose of activities of monitoring, audits and inspections is to confirm:

- Protection of human subjects is adequate
- Accuracy, completeness and verification of reported results and the process of generating the results
- Compliance with defined procedures and (local) legal and regulatory requirements.

The distinction between these different activities lies in the responsibilities of different parties and the different frequencies for the conduct of these activities:

- Monitoring is the ongoing act of overseeing the progress of a study, and ensuring that it is conducted, recorded, and reported in accordance with the protocol, procedures and regulatory requirement(s). Typically a monitor will assess failure of protocol compliance, failure to keep adequate and accurate records, problems with the informed consent form and, as applicable and, specifically, failure to report adverse events. If applicable, regular source document verification avoids numerous queries and late database problems.
- Auditing is independent examinations of study-related activities and documents to determine whether they were conducted, and the data were recorded, analysed, and accurately reported according to the protocol procedures and the applicable regulatory requirement(s). Audits can be internal (audits organized by the same organisation that is subject to the audit) or external (for example audits of service providers used for study related activities)
- Inspections are essentially audits carried out by competent authorities.

For monitoring and audits to be effective, their planning and scope is defined upfront and documented in monitoring and audit plans. Their output should be documented in their respective reports.

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In response to issues identified in monitoring and audit reports, continuous quality improvement is achieved by performing a root cause analysis and, as appropriate, preventive and corrective actions should be implemented. Structural implementation is best achieved by amending or creation of standard operating procedures and templates.

In addition, effective policies and procedures must be in place to deal with fraud/misconduct/non-compliances and all staff must be trained to report such issues.

Contracts should allow conducting monitoring, audits and inspections between parties, specifically in the case of a legal requirement for any party involved to perform such activities during or within a reasonable period after the study was conducted.

Key elements for implementation:

- i. Monitoring audit and inspection readiness plans available
- ii. Periodic internal audit performed
- iii. Documentation of monitoring and audit reports and results
- iv. A process for deviation management in place; corrective and preventive actions and follow-up

6.7.11. Contracting

Organisations can outsource (parts of) the activities to 'service providers', but the ultimate responsibility remains with those contracting the services. Before starting the process of contracting other parties ('service providers') to perform the work, outsourcing requirements, timing of deliverables and responsibilities need to be determined, so that the quality management for product or service obtained from other partners can be established.

Selection criteria and decision rationale must be determined for all (sub)contractors and the capabilities of selected potential contractors must be assessed and documented against those criteria. Specific attention should be paid to process and criteria of subcontracted activities by the primary contracted party (such as for database hosting or software).


A confidentiality agreement must be established between parties prior to disclosing any proprietary information.

The contract must describe clearly who is responsible for each step of the outsourced activity, including, if applicable, safety data collection and reporting.

If case committees (i.e. adjudication committees) are assigned to a study, appropriate contracts defining their responsibilities and timelines of the activities and confidentiality should be put in place.

Key elements for implementation:

- i. Documented process of selection of contracted parties and criteria for assessment
- ii. Plans for ongoing oversight, including communication and escalation plans
- iii. Confidentiality and contractual agreements in place which defines the set of outsourced activities and timelines of deliverables

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6.8. References, additional readings and listing of applicable legislation and regulation

6.8.1. References

- [1] ISO 9000:2015 3.6.2
- [2] October 2008 presentation on CTTI by Dr. Rachel Behrman, CTTI Co-chair and then Associate Commissioner for Clinical Programs
- [3] ENCePP Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide6.shtml, accessed 12 Oct 2016
- [4] Good pharmacovigilance practices (GVP) Modules VIII Post-authorisation safety studies (Rev 2) (EMA/813938/2011 Rev 2, 4 August 2016)
- [5] DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
- [6] Guidelines for good pharmacoepidemiology practice (GPP), Pharmacoepidemiology and Drug Safety, 2016; 25: 2–10 (for the survey the 2008 guidelines were used Pharmacoepidemiology and drug safety 2008; 17: 200–208)
- [7] Good Epidemiological guidelines (GEP) , IEA guidelines for proper conduct in epidemiologic Research, November, 2007, <http://ieaweb.org/good-epidemiological-practice-gep/>
- [8] Good pharmacovigilance practices (GVP) Module I Pharmacovigilance systems and their quality systems EMA/541760/2011
- [9] Council for International Organizations of Medical Sciences (CIOMS) International ethical guidelines for epidemiological studies, 2002.
- [10] ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Chapter 6: Quality management. http://www.encepp.eu/standards_and_guidances/methodologicalGuide6.shtml
- [11] Guidelines for good database selection and use in pharmacoepidemiology research. (Pharmacoepidemiol Drug Saf. 2012 Jan;21(1):1-10. Erratum in: Pharmacoepidemiol Drug Saf. 2012 Nov;21(11):1249)
- [12] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344-9. PMID: 18313558
- [13] Eudralex 11: Computerized systems. http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/anx11_en.pdf
- [14] ISO Standards http://www.iso.org/iso/home/store/catalogue_ics.htm
- [15] International Conference of Harmonization Guideline for Good Clinical Practice (GCP) E6(R1), Current Step 4 version, dated 10 June 1996
- [16] Quality assurance and quality control in longitudinal studies (Epidemiol Rev. 1998;20(1):71-80)
- [17] Reflection paper on risk based quality management in clinical trials EMA/269011/2013 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf

6.8.2. Additional readings

- Bhatt A. Quality of clinical trials: A moving target. Perspectives in Clinical Research. 2011;2(4):124-128. doi:10.4103/2229-3485.86880
- Patel K, Chotai N. Documentation and Records: Harmonized GMP Requirements. Journal of Young Pharmacists: JYP. 2011;3(2):138-150. doi:10.4103/0975-1483.80303.

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- Haleem RM, Salem MY, Fatahallah FA, Abdelfattah LE. Quality in the pharmaceutical industry – A literature review. Saudi Pharmaceutical Journal: SPJ. 2015;23(5):463-469. doi:10.1016/j.jsps.2013.11.004. Standards for Data Management and Analytic Processes in the Office of Surveillance and Epidemiology FDA MAPP 6700.2, Effective Date: 3/3/2008
- Good Research Practice for Observational Studies of Comparative Effectiveness (GRACE) https://www.graceprinciples.org/doc/GRACE_Principles_10April2010.pdf
- Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf>


6.8.3. Listing of regulation and legislation

EU legislation and regulation applicable for observational studies:

- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
- WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 2013


Legislation applicable to MAH and/or regulatory bodies:

- Regulation (EC) No 726/2004
 - Directive 2001/83/EC
 - Commission Implementing Regulation (EU) No 520/2012)
 - Good pharmacovigilance practices (GVP)
 - o Module I - Pharmacovigilance systems and their quality systems EMA/541760/2011
 - o Module VI – Management and reporting of adverse reactions to medicinal products EMA/873138/201
 - o Module VIII - Post-authorisation safety studies EMA/813938/2011
- For latest versions of the GVP: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

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7. Module 4. Communication recommendations

This module has been submitted separately as Deliverables 1.7 (Analysis of key issues and gaps about perception and knowledge on benefits and risks of vaccines) and 1.12 (Strategy for public communication in the context of vaccine benefit-risk monitoring). The recommendations included in these deliverables will be reviewed by WP7 for implementability and feasibility and therefore are still subject to change. These recommendations will be integrated into the good practice guidance as part of the ADVANCE blueprint following their finalisation.

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8. Discussion

The aim pursued by ADVANCE in the development of good practice guidance has been to provide standard principles by which studies initiated, managed or sponsored by academic institutions, public health authority or vaccines will be conducted through the ADVANCE infrastructure, either directly or via third parties (ADVANCE Full Project Proposal:115557-2).


Of the four modules included in this Deliverable, three were planned at the start of the project (Code of conduct, Governance models, Communication recommendations) whilst the recommendations on quality management have been added during the course of the development of the good practice guide. This addition was based on comments received from patients' and health care professionals' representatives at the ADVANCE WP1 workshop on 13-14 November 2014, who suggested that having confidence in the quality of the study would be an important element for them to have confidence in its results. A specific group was therefore created within WP1. The development of minimum quality requirements was the approach developed in a first phase but discussions within the consortium and the results of the survey reported in this document revealed that *imposing* minimum requirements might be a too ambitious approach and could discourage research centres with relevant expertise to participate in studies if these requirements proved to be too demanding. Subsequently, the approach was taken to provide recommendations on the quality management aspects of studies which should be considered "minimum good practice" and which all research centres should aspire to if they do not apply them already.

In its current status, this good practice guidance contains four different modules developed separately. They still need further work in terms of consultation, testing and review by the ADVANCE WP7 as to their implementability and feasibility.

In addition:

- It is planned to submit the Code of conduct in a peer review journal (e.g. Vaccine); this submission will give the opportunity to receive comments from reviewers external to the project, and the dissemination of the text, if accepted for publication, will stimulate further discussions.
- Further work will be performed on the Governance models including the development of a research contract template for each governance model, and a workshop to be organised by IMI with a large range of stakeholders.
- Quality aspects have been introduced in the proof-of-concept studies and will be subject to a review of their implementation and of any concerns that may be associated with their use in terms of resources. A public consultation will be considered by the ADVANCE consortium.
- Results from the ADVANCE work on Communication recommendations will be submitted for publication. As the objectives of this work include the development of a strategy on how to communicate results of studies of vaccine, the communication recommendations will be applied to the results of the POC studies and a "mock-up" communication will be tested with the public, patient representatives and health care professional representatives.

The four Modules of the good practice guidance will be ultimately integrated in the final ADVANCE Blueprint.


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9. ANNEX 1. Compilation of comments on ADVANCE Code of Conduct received during the public consultation


The column ID indicates a sequential number of the respondents.

1. General comments


ID	General comment
1.	<p><Since the 2007 good pharmacoepi guidance, we have an increasing number of guidances in order to improve research. This includes several ENCePP guidances. In addition there is strobe, consort stratos etc. And now ADVANCE.</p> <p>To our centre, these guidances make little sense as long as adherence remains voluntary. ></p>
2.	<p><The document reflects the "best state of art" for the conduction of any scientific study. I have no specific comment. On the matter of benefits/risks of vaccines I am sceptical on the acceptability of results by health care "consumers" and patients associations, whatever the quality of scientific work. Good communication on the topic will probably be even more difficult that good research. I would suggest contact at the very early stage of any research with the relevant associations. ></p>
4.	<p><I find it very good, it sounds operational, my main remark is that this CoC should become a systematic practice, integrated within a policy, for all the studies within the same institution. I do not see how for the same vaccine, studies may be developed in Europe or elsewhere based on this CoC or on others within the same institution></p>
8.	<p><1. The recommendations to implement scientific independence contradict the ENCePP CoC provisions (in italics) which require that any party with a financial, commercial etc. interest cannot be part of the research team: <i>'Once the protocol has been finalised, no person with a financial, commercial or personal interest in a particular outcome of the study shall take part in any study activity that could influence the results or interpretation thereof in any particular direction;'</i> <i>'The (primary) lead investigator has the unrestricted freedom of independent publication of the study results irrespective of data ownership;'</i> conflicts with the ADVANACE CoC provision in point 33 where the research contract 'should' include an <u>independent</u> publication policy.... this should rather be 'must' and the use of should vs must throughout the whole document should be reviewed (see also specific comments on text)</p> <p>2. It should not be called a 'code of conduct' to avoid confusion with the ENCePP CoC, rather a 'good practice guidance on scientific integrity in collaborative studies'.</p>

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	<p>3. Why is a new code of conduct needed for vaccine studies? It's possible that guidelines are needed to involve industry in such research beyond protocol finalisation but then the ADVANCE guide should focus on transparency and scientific integrity because scientific independence cannot be achieved.</p> <p>4. There is no mention of the ENCePP Seal which is promoting scientific independence. There is no reason why this is any less desirable for vaccine studies.</p> <p>5. There is a need for proof-reading how 'should' and 'must' were used in line with the introduction in particular when the document is read in a hurry. There are areas where should has to be replaced with must.></p>
13.	<p>1. Comment: Text is very general Proposed change: Clarify why these guidelines are "general", e.g. to find common ground; based on principles; decision to leave operational details out;</p> <p>2. Comment: "Not clear why this document is necessary. There is nothing specific to Vaccines in this document." Proposed change (if any): Highlight that what is specific for vaccines is the need for partnership/collaborative studies, mostly because many post-marketing disease surveillance and vaccination data are owned by multiple types of organisations. Explain that there is no existing code of conduct for this need and type of collaboration; all other, existing alternatives have shortcomings. Clarify that the aim is to find a common ground and commonly acceptable set of rules between all major stakeholders. We propose to add a specific section: « Why do we need this Code of Conduct ».</p> <p>3. Explain somewhere that MAHs have specific obligations from the GVP;</p> <p>4. Comment: Why no reference to CIOMS – Ethical guidance for conduct of Epidemiological researches?</p> <p>5. Preposition to use with "participate" is "in" not "to". Proposed change (if any): – change throughout document;</p> <p>6. Suggest preceding "timelines" by "planned". Proposed change (if any): – change throughout document.</p>
14.	In general, the Code does not make clear that data is shared within Europe between various databases inter-member states. It could mention also that should data be shared with participants beyond Europe, processing of such data will be subject to the applicable local or European data privacy regulations.
15.	1. For the studies that follow this code of conduct, reports should be able to have an ADVANCE stamp;

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	2. It seems that all items of this guidance are applied to epi studies of drugs as well. It would be good to highlight the guidance that is specific for the characteristics of the field of vaccines.
16.	<p>1. The document draft is very complete, and at the same time is very brief.</p> <p>2. It would be a great idea more consensus with the WHO and their division dedicated to vaccines and biologicals, the opinion of UNICEF and the opinion of PAHO, because is well known that the most successful immunizations programmes are on the Americas Regions.</p> <p>3. The opinion and disclosures of the industry of vaccines and from MOH of the countries of Europe is necessary for a more complete picture on the opinion of all the partners of those products.</p> <p>4. The issues of impact evaluations and pharmacoeconomics evaluations are not covered in the document, it is possible that some considerations would be provided in the future in terms of annexes.</p> <p>5. In summary, for my reading and peer review process have being very useful and agreeable.</p>
17.	<p>1. The document on the governance models should be integrated in the Code of Conduct and exposed to a public consultation in an integrated fashion. The document on governance models should cover all aspects of decision making and conflict resolutions internal to the study team, as well as the mechanisms for data custody and sharing, both internal and external to the study team;</p> <p>2. Besides individual responsibility and CoI, interests of organizations should be explicitly tackled (decisions about who makes the study);</p> <p>3. Qualified research organizations should be involved in the studies, regardless of previous disagreements on study results with study funders., To ensure this public interest, a transparent process of recruitment of study organizations should be put in place, where the ultimate choice does not rely solely in the hands of the sponsor;</p> <p>4. Whenever possible, the analytical dataset should be made public or anyway accessible to the scientific community for re-analysis.</p>
18.	<p>1. The draft code of conduct we believe is an important document in furthering the governance principles germane to the health care arena and (re)use of health data for medical research, and believe there are many generic principles not only specific just to vaccines. This process also underlines the need for public-private consortia to have adequate governance principles, supporting scientific independence, transparency and public trust, which again is not specific only to the vaccines arena.</p> <p>2. As such EMIF is amenable to publicly supporting the ADVANCE draft code of conduct, as well as to exploring how best to collaborate and incorporate those principles applicable to both our programmes where relevant.</p>
19.	1. This is a largely well written manuscript. A few specific suggestions are given below.

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2. It could be further improved if the nature of recommendations could be more objective rather than subjective as it is now.

3. The manuscript/guidelines could refer to existing resources while recommending something. It is not needed to prepare new set of documents 'de-novo'. It currently has insufficient reference to the existing available guidelines and resources.


- 20.**
1. While transparency as a basic principle is supported, the proposed level of public disclosure of various documents throughout the COC raises several general concerns over:
 - Timely execution, especially when considering that the code would be used for rapid B/R evaluation in which case legal release etc. of these disclosures may prove a bottle neck in the study implementation.
 - The impact of public disclosure on the "openness" of the comments from (internal and external) reviewers at every step of the design and reporting phase. Reviewers could become concerned with the public perception of their comments.
 - Feasibility - Having various locations to disclose the proposed documents (for various parties, but even for various documents for a single study) would not support transparency. Current available repositories/registries/journals would need to accommodate to support bringing together these various documents in order to achieve transparency.
 - Intellectual property. Originally public registries were implemented for patients with rare disease to seek possibilities for experimental treatment. This has shifted to support the principle of complete transparency, but has at the same time raised concern over intellectual property, privacy and competitive principles/requirements. The compatibility of the proposed disclosures with these aspects will need to be determined and reasonably balanced and driven not only by the principle of transparency but also by the purpose and potential impact of the information provided.
 - Disclosure specifically of the full report on a public repository may impact compatibility with IP and conditions to allow journal publications. Complete transparency is not necessarily the same as disclosure of all and every detail. This may not always support the public trust if comments cannot be understood by the audience. Especially for negative information. Internet has the ability to express emotional responses promptly with consequences as a result. It should therefore be possible to provide summary information to specific audiences in public repositories.
 2. On (potential) conflict of interest and scientific independence. The CoC appropriately identifies that conflict of interest is not necessarily only caused by financial or commercial interest. To support unambiguous interpretation an explicit clarification would be needed on that, since conflict of interest can affect all those involved, it should not be the aim to avoid conflict of interest but should be appropriately managed (as stated) and that it should not exclude parties from participation.
 3. Proposed external reviews need to take into consideration that this is potentially added to Regulatory required review or specify that regulatory review also is classified as external review.

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4. The scope of the provisions of the CoC are difficult to expand to those who are not part of the research contract. If the scope of transparency would include public disclosure of comments from regulatory bodies, this would need to take into account additional considerations on the regulatory process.
A similar situation applies to comments from journal reviewers. Comments from both these sources are however currently not made publicly available.
5. Are the proposed principles of data sharing compatible with current regulations, data privacy, rules of market competition and IP? We would suggest a review of the CoC by legal experts in this field.
6. Aspects of external audit and control are not addressed.
7. More than 32 clauses of 50 pertain to "must". In the situation of a public crisis, further flexibility should be introduced.

2. Specific comments on text


ID	Line number(s) of the relevant text	Comment and rationale; proposed changes
3	155-157	Comment: < How will this work? How?> Proposed change: -
3	163-164	Comment: <? needs clarification. If the roles of all those involved in the study are well defined who are the other parties involved> Proposed change: -
3	169	Comment: - Proposed change: <Protocol posting on public website before study data collection or extraction commences >
3	187	Comment: < I agree that those with more senior roles should be experienced but? all> Proposed change: -
3	230	Comment: <? care with wording as in some primary data studies 'participants' are those recruited!> Proposed change: -
3	247	Comment: Pleased to see this as a heading. I would like to see more clarification of financial COI. It is still often only seen as related to commercial funding. The possible influence on funding of academics or academic departments from any source should also be reported.

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		Proposed change: -
3	274-275	Comment: < Sense check? An amendment should describe developments during a study or are these sometimes more appropriate in the report. E.G. validation of an algorithm> Proposed change: -
3	277-278	Comment: <There are a few other headings that should be demonstrated as per other ENCePP guidance> Proposed change: -
3	284-285	Comment: < Based on knowledge at the time which sometimes means predicting uptake> Proposed change: -
3	291-293	Comment: < Is the document addressing PASS studies? If so could there be an allowance for the fact that these protocols might be written several years before the launch of the vaccine and before the schedule for vaccination is known. None key people, code lists, definitions... might be out of date if written at the initial protocol stage. I suggest an option for including a plan for updates. The requirement for great detail some time before the study starts will result in amendments which require additional time for all involved including the EMA. Could there be more flexibility here. Some of this detail may be in the SAP which will be required by the EMA shortly I believe> Proposed change: -
3	309	Comment: - Proposed change: <data collection or the first cut of data for this study>
3	342	Comment: - Proposed change: < Any deviations from the protocol or statistical analysis plan must be clearly documented in >
3	352	Comment: < When appropriate – given issues of multiple analyses. Again these should be in the SAP or reasons for the additional analysis explained.> Proposed change: -
3	369-370	Comment: < What if there was no agreement to publish in advance but there is an interim finding that has public health implications > Proposed change: -
3	405	Comment: < Within a specified period > Proposed change: -
3	407	Comment: <Relevant to what and to whom. Can this be more clearly defined with regard to the protocol and SAP> Proposed change: -
3	475	Comment: - Proposed change: (or another person) within the original study team to verify the compliance of the request
3	477	Comment: <Perhaps these terms need explanation. Do they include the owner of the original secondary data?>

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		Proposed change: -
3	506	Comment: < I suggest that there were good points about the contract earlier in the document which are not explained here> Proposed change: -
3	510	Comment: <But all must be covered by a contract> Proposed change: -
4	74	Comment: <The question is also, on top of the conduct of a given study, the planning of a set of studies needed to monitor the B/R of a given vaccine, with a clear indication that these are exhaustive plans (could be revised regularly). i.e., studies which are not echoing the plan should not be conducted. There is some indication on this in GVP modules, and also see section 15 in the EFPIA code: which post marketing observational studies could be of scientific value and not contribute to B/R assessment? I think very few. Thus the EFPIA code for studies on vaccines should probably follow Advance CoC.> < Institutions should have policy with regard to CoC: all their studies should comply: not only some and not others>. Proposed change: -
4	136	Comment: < More generally research questions (plural) triggered by the use of the vaccine or type of vaccines > Proposed change: -
4	137	Comment: <Yes, this echoes the comment1: prioritisation is relative to other studies for a given vaccine> Proposed change: -
4	147	Comment: - Proposed change: < (including identification of the research question, translation of the research question into a study....)>
4	150	Comment: see the following comment in line number 154 Proposed change: -
4	154	Comment: < I would say also 'income' of the study: the fact itself that a study is conducted on a given question, must not be biased, but biased on evidence or monitoring needs> Proposed change: -
4	156	Comment :< How is the study team composition decided? Is it sponsor initiated, investigator initiated, are scientists from companies part of the team?> Proposed change: -
4	157	Comment: < We could consider that for both oral communications and publications, all members of the study team should declare that conduct and analysis is their responsibility and not that of their institution (including for companies)> Proposed change: -
4	158	Comment: < Also, companies should designate a 'responsible pharmacoepidemiologist', similar to the responsible pharmacist and the QPPV, that would be responsible to ensure independence of study results> Proposed change: -

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4	164	Comment: < We should clarify which other parties could be involved: regulatory bodies, national authorities, funders, others?> Proposed change: -
4	167	Comment: < External advisory board should be independent from companies “board of experts”> Proposed change: -
4	169	Comment: < In 7, 33, requester funder is entitled to view the results and interpretation and provide comments. This mean they are entitled to review? Here again, it is clear that if an epi from a company is part of the study team, he/she should have means to be independent within the company, and not to translate comments resulting from within company review by many companies’ stakeholders (e.g. medical to market to legal)> Proposed change: -
4	188	Comment: - Proposed change: < All researchers involved in the study team must be involved (!) i.e. no madarin) qualified and ...>
4	189	Comment: <Yes, does it preclude PhD students or post doc to be part of the team? Hope not>; <Important to document % of time devoted to the study> Proposed change: -
4	198	Comment: - Proposed change: < pharmacoepidemiological practices, and GVP modules without restriction. It must ensure that...>
4	220	Comment: <This should be true for a given study, as for institutions: university xx and company yy should have internal policy of registration of all their studies> Proposed change: -
4	222	Comment :< Suggest another point: every study should be qualified as regard to GVP (i.e. PAES, PASS, etc...> Proposed change: -
4	227	Comment: - Proposed change: <committee must be publicly disclosed at an early stage of the study and updated. Potential...>
4	256	Comment: < CoI can be at individual and institutional level. Academic research/policy can be evaluated on their capacity to attract external funding. A ratio of external funding could be an indicator of independence rather than of excellence only> Proposed change: -
4	306	Comment:<Also qualification of the study / GVP> Proposed change: -
4	309	Comment: <Thus should not be eligible to co-author the paper (would be important to be explicit)> Proposed change: -
4	310	Comment: <There can be studies with experimental design and we should protect innovation, thus may not be always applicable, also be sure this will not compromise publication of the study results, possible pb with editors’ copyrights>

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		Proposed change: -
4	340	Comment: <List of persons rather than institutions> Proposed change: -
4	366	Comment: <Should, this is for scientific quality of the study> Proposed change: -
4	378	Comment: <i.e. No co-authors of the publications> Proposed change: -
4	380	Comment: <Check possible drawback on publication in scientific journals> Proposed change: -
4	405	Comment: <All members of the study team eligible for authorship should co-author the paper (not allowed to resign from authorship)> Proposed change: -
4	464	Comment: <This is larger, and is also sharing of data; for example, when a team plan to analyse passive pharmacovigilance data, there should be a protocol etc.;> Proposed change: -
5	90-92	Comment: <Regarding "Background information for the consultation." "These various guidelines, as well as articles identified from a literature review, were analysed and used as a starting point for the development of the ADVANCE code of conduct."> Proposed change (if any): <A separate document is needed with full description of conductors, methods, and results of the "literature review," including the PRISMA check list and diagram.>
5	92-94	Comment: <Regarding Background information for the consultation." "However, it was considered that none of them fulfilled all the needs of the post-authorisation benefit-risk monitoring of vaccines or could be used as a stand-alone reference to ADVANCE."> Proposed change (if any): <Methods and criteria used for reaching the decision that "none of them fulfilled all the needs" should be mentioned.>
5	114-116	Comment: <Regarding "THE ADVANCE CODE OF CONDUCT. A. Introduction." "The ADVANCE Code of Conduct has been written by the ADVANCE consortium, a public-private partnership established to improve public health through a scientific and transparent framework for the rapid monitoring of the benefits and risks of marketed vaccines.">

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		Proposed change (if any): <Names and organizational affiliation of the authors of the current document should be provided within the document.>
5	124-125	Comment: <Regarding "THE ADVANCE CODE OF CONDUCT. A. Introduction." "The ADVANCE Code of Conduct should be adopted voluntarily by all parties involved in a study and it should be adopted entirely."> Proposed change (if any): <The language is too strong for a scientific environment.>
5	126-128	Comment: <Regarding "THE ADVANCE CODE OF CONDUCT. A. Introduction." "Recommendations that are considered to be uniformly applicable are identifiable by the modal verb "must" and those that should be considered for implementation are identifiable by the modal verb "should"."> Proposed change (if any): <As these are scientific and evidence-based recommendations, details of the methods and results for grading quality of evidence and strength of recommendations (i.e. must versus should) should be provided. >
5	134	Comment: <Regarding "THE ADVANCE CODE OF CONDUCT. B. Guiding principles. Footnote number three." "See section 4.2 of the following document for an additional description of these guiding principles: http://www.advance-vaccines.eu/app/archivos/publicacion/7/ADVANCE_WP1_Deliverable-1_6_V5-Final.pdf "> Proposed change (if any): <Description of the guiding principles should be provided in an appendix of this same current document.>
5	151-154	Comment: <Regarding "C. Recommendations. 1. Scientific independence. Recommendations." "1. The study design, methods of data collection, data analysis, interpretation of the results, study report and publications must be based only on robust scientific criteria without undue influence of any financial, commercial, institutional or personal interest in a particular outcome of the research."> Proposed change (if any): <(a) Criteria for delimitation of "undue" versus "due" influence of "any financial, commercial, institutional or personal interest in a particular outcome of the research" should be explicitly mentioned. (b) Provision of relevant details about scientific

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		independence and disclosure of potential conflict of interests for the current document can set an example of application of the recommendation on scientific independence.>
5	158-171	<p>Comment: <Regarding "C. Recommendations. 1. Scientific independence." "3. The recommendations of the ADVANCE CoC are necessary and sufficient to safeguard scientific independence; in particular: ...".></p> <p>Proposed change (if any): <Provision of relevant details about the four items under this recommendation can set an example of application of the recommendation on scientific independence.></p>
5	172	<p>Comment: <Regarding "C. Recommendations. 1. Scientific independence. Additional reading."></p> <p>Proposed change (if any): <This document needs citations to published references.></p>
5	187	<p>Comment: <Regarding "2. Scientific integrity. Recommendations." "5. All researchers involved in the study team must be qualified and experienced scientists."></p> <p>Proposed change (if any): < (a) Who verifies the qualifications and experience of the scientists involved in the study team? (b) What are the explicit criteria for the qualifications and experience of the scientists involved in the study team?></p>
5	188	<p>Comment: <Regarding "2. Scientific integrity. Recommendations." "6. All researchers must act in accordance with the values of science, including: - Accuracy (reporting findings precisely and preventing errors)".></p> <p>Proposed change (if any): <(a) What are the "must" and "should" levels of statistical accuracy (sampling errors, estimation errors)? (b) What are the "must" and "should" levels of residual confounding errors that might not be taken out from study results even using the most rigorous statistical analysis methods?></p>
5	194-198	<p>Comment: <Regarding "2. Scientific integrity. Recommendations." "7. The study team is responsible and accountable for the integrity and validity of its work. The study team should adhere to Good epidemiological practices and Good pharmacoepidemiological</p>

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		practices, without restriction. It must ensure that its work is performed objectively, using the most appropriate techniques. The research must be factual, transparent and designed objectively to answer the appropriate questions."> Proposed change (if any): <Reference citations are needed for "Good epidemiological practices and Good pharmacoepidemiological practices.">
5	213	Comment: <Regarding "3. Transparency".> Proposed change (if any): <The funders should have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No individuals employed or contracted by the funders played any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.>
5	217-220	Comment: <Regarding "3. Transparency. Recommendations. 7."> Proposed change (if any): <(a) As the recommendations are numbered consecutively, there is already a recommendation number seven in line 194. Numbering of this recommendation number 7 in line 217 seems wrong. (b) The footnote for this recommendation, i.e. "6 The EU PAS Register may be used for the purpose of study registration in a public database (http://www.encepp.eu).> recommends researchers from United States to register their studies in a non-US study register. What would be the proportion of the audience that would abide by this recommendation? >
5	217-220	Comment: <Regarding "3. Transparency. Recommendation number 7. Footnote number 6.">"Primary data collection: data collection directly from healthcare professionals or consumers (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care).> > Proposed change (if any): <Retrospective observational studies (i.e. retrospective cohort, retrospective case control, and their derivatives) should be included.>
5	319-320	Comment: <Regarding "5. Study protocol. Recommendations." "24. Key statistical analyses should be described in the study protocol. A detailed statistical analysis plan should be finalised before the end of data collection or extraction.">

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		Proposed change (if any): <(a) Methods to be used for verification of assumptions of statistical tests and models should be mentioned. (b) Methods to be used for handling missing values should be mentioned.>
5	331	<p>Comment: <Regarding "6. Study report."></p> <p>Proposed change (if any): < (a) In case of primary data collection, numbers and percentages of eligible participants who did not consent to participate, and those who revoked their consent in each stage of study should be reported. (b) The following elements of design - inter alia - should be included in study reporting:</p> <ol style="list-style-type: none"> 1. Study countries and place(s) 2. Study start and end year and month 3. Study objective and hypothesis 4. Study design 5. Vaccine type(s) in study group(s) 6. Vaccine manufacturer 7. Adverse Events Following Immunization (AEFIs) names 8. AEFIs definitions 9. AEFIs diagnostic criteria 10. AEFIs grading of severity 11. Time interval coverage from vaccination to AEFIs 12. Occurrence time of AEFIs 13. Participants' age 14. Participants' sex 15. Participants' healthy or diseased status 16. Number participants included in statistical analysis 17. Number participants who experienced the AEFIs 18. Causal association assessment method used 19. Causal association assessment results 20. Association measure(s) values and uncertainty limits 21. Rechallenge test if applicable>
5	438-447	Comment:

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		<Regarding "8. Subject privacy. Recommendations 38 and 39."> Proposed change (if any): <The recommendations refer to European laws and regulations only. What about studies elsewhere?>
6	102-106	Comment: - Proposed change (if any): < The objective of this public consultation is to collect the views of the different actors investigators involved in clinical and research studies on the benefits and risks of vaccines by and of investigators professionals experienced in the design and conduct of pharmacologic epidemiological studies. involving different partners. A consensus between all concerned stakeholders will accelerate the initiation and conduct of high quality observational vaccine studies.>
6	109	Comment: - Proposed change (if any): < using the template. Please indicate if you are responding on behalf of an organization>
6	118	Comment: - Proposed change (if any): <organizations but it may also be used for other types of studies, such as self->
6	123	Comment: - Proposed change (if any): <The ADVANCE Code of Conduct applies to all individuals and organizations>
6	125 -126	Comment: - Proposed change (if any): < The ADVANCE Code of Conduct should be adopted voluntarily and entirely by all parties involved in a study. and it should be adopted entirely >
6	137	Comment: - Proposed change (if any): <research question, applying the appropriate scientific methods with integrity and thoroughness.>
6	159	Comment: The recommendations of the ADVANCE CoC (need to spell this out) Proposed change (if any):
6	185-187	Comment: - Proposed change (if any): <Scientific integrity is acting in accordance with the values of science, such as truthfulness, honesty and open reporting, even when no one is monitoring looking over the researcher investigator. shoulder. >
6	226	Comment: Declarations of Interests (DoI) (spell out)

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		Proposed change (if any): -
6	274-276	Comment: - Proposed change (if any): < Document containing all the technical details of the design, implementation, analysis, documentation and publication of the results of an epidemiological study, including timelines should be part of research document. The study protocol includes all the procedures developed or used>
6	305-306	Comment: - Proposed change (if any): < A specific section must describe the regulatory obligations and recommendations applicable to the study, with a rationale for their use in a specific protocol.>
6	366-367	Comment: - Proposed change (if any): < the secondary user of data. The data custodian(s) should may be invited to provide comments based on their knowledge and experience with the data.>
6	410	Comment: - Proposed change (if any): <Information published must be accurate and complete. Under In no circumstances should the>
6	472	Comment: - Proposed change (if any): <Data should be shared only after the study report has been finalized.>
6	490	Comment: - Proposed change (if any): <in the context of an audit by a recognized competent authority.>
7	394-399 (rec.32)	Comment: <Also inconclusive results should be published, as prescribed by WMA Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (2013) para. 36 > Proposed change (if any): <Publication of the results of studies, whether positive, negative, or inconclusive is for the benefit of the scientific and public health community and attempts must be made to publish as soon as possible results in a peer-reviewed scientific journal. Presentations at meetings are not substitutes for publications in peer reviewed literature. The study report or summary of the main results of the study must be included in the publicly accessible study register where the study is registered.>
7	A new recommendation 33	Comment: <New recommendation n ° 33 to be included: <33. All sources of funding, affiliations and conflicts of interest must be published along with the study results.> Proposed change (if any):
7	407-410	Comments:

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	(rec. 34)	<p><1. This paragraph should go first in the list of recommendations as it is the most important statement. 2. No distinction should be made whether study results are relevant or not. They should ALL be published. 3. Also inconclusive results should be published, as prescribed by the WMA Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (2013) para. 36 (as stated above) ></p> <p>Proposed change (if any): < All relevant study results must be made publicly available, irrespective of the results, whether positive, negative or inconclusive. Information published must be accurate and complete. In no circumstances should the results be changed. Unless there is an urgent public health issue, the results of a study should undergo independent peer review before they are made public or the media are informed.></p>
7	467-469 (rec. 40)	<p>Comment: <Anonymized data should be the rule, and identifiable data the exception. Recommendation n°40 should state it clearly.></p> <p>Proposed change (if any): <There should be an open and collaborative approach to study data sharing with persons from outside the study team. Data sharing will normally concern only the anonymised analytical dataset. Only in exceptional and justified cases can the data be identifiable.></p>
7	471-478 (rec. 42)	<p>Comment: <The reference to "Another person" is vague. We would recommend to clarify who is exactly in charge. ></p> <p>Proposed change (if any): -</p>
7	479-488	<p>Comment, The notion of "interest for public health" is very broad and can be given a wide margin of interpretation. Further clarification might be needed here. ></p> <p>Proposed change (if any): -</p>
8	401-403	<p>Comment: < this <i>should</i> rather be 'must' and the use of should vs must throughout the whole document should be reviewed></p> <p>Proposed change (if any): <The research contract should must include an <u>independent</u> publication policy allowing the principal investigator and relevant study team members to independently prepare publications based on the study results irrespective of the funding or data source>.</p>
8	517	<p>Comment: <regarding the Research contract there is no mention that the remuneration shall ... shall not depend on the study results></p> <p>Proposed change (if any): -</p>

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9	79		Comment: <add a fifth area to the four areas of recommendations> Proposed change (if any): add a fifth area addressing: <Emergency information – such as the flu epidemics.>
9	235-236		Comment: <addition to contemplate the collection of secondary data. > Proposed change (if any): add <In case of secondary data collection, the subjects who participated should be informed on when the results of the research will be published and should receive access to them when they are made available.>
9	394-406 (rec 32-33)		Comment: <The publication policy should go in line with Regulation 2014/536 on Clinical Trials. The Regulation establishes that “the results of the clinical trial should be reported within one year from the end of the clinical trial.” (Recital 37)> Proposed change (if any): -
9	411-413 (rec 35)		Comment: <This Recommendation should be reviewed in line with Regulation 2014/536 on Clinical Trials to ensure that there is no contradiction with an already adopted legislation. > Proposed change (if any): -
9	465 (rec 41)		Comment: <Is this Recommendation contrary to lines 462, 463, 464?> Proposed change (if any): -
9	479-488 (rec 43)		Comment: <Add a fourth bullet point covering an additional justification. > Proposed change (if any): addition of a fourth bullet point to include <in case of an emergency such as the Ebola crisis and the search for a vaccine.>
10	187		Comment: <In order to allow early-career people (who might be qualified but not experienced) to participate, consider deleting “and experienced.”> Proposed change (if any): < All researchers involved in the study team must be qualified and experienced scientists.>
10	190		Comment: <How about “Accuracy (reporting findings accurately and completely)”?> Proposed change (if any) :< Accuracy (reporting findings precisely and preventing errors accurately and completely)>
10	196		Comment: <Instead of “without restriction,” do you mean “without exception”? I didn’t understand the former wording> Proposed change (if any): -
10	223		Comment: <By “non-financial support,” do you mean things like provision of computers or lab space by an institution? If so, consider replacing “financial and non-financial” with “material.” > Proposed change (if any): < financial and non-financial material public and private supports for the study should be documented.>
10	250-251		Comment: -

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		Proposed change (if any): < or personal interest sufficient that might reasonably be expected to influence the objective-exercise of his/her judgment towards regarding any activity of the project.>
10	254	Comment: <Before “academic competition,” consider adding “involvement in other scientific studies.”> Proposed change (if any): <relationships, involvement in other scientific studies, academic competition or beliefs.>
10	270 (section 5)	Comment: <it would be good to add an item that the protocol should (not must) contain an approximate estimate of the statistical power expected to exist to answer the main study question and/or to detect a RR or AR of X.> Proposed change (if any): -
10	331 (section 6)	Comment: <Similarly, if the results are null, add that the study report should (not must) contain at least a qualitative statement about the statistical power such that the reader can get a sense of whether the null results are believable or rather a consequence of insufficient power.> Proposed change (if any): -
11	319-320	Comment: <The new Clinical Trial Regulation 536/2014 will require population group breakdown by gender and age. This is important because women and men respond differently to vaccines, as do older people. Proposed change (if any): <Key statistical analyses should be described in the study protocol including gender and age breakdown as required by the Clinical Trial Regulation 536/2014. A detailed statistical analysis plan should be finalised before the end of data collection or extraction.>
12	74	Comment: <Observational studies only or to limit to vaccine benefit-risk monitoring activities but not all studies> Proposed change (if any): -
12	121	Comment:< add the word “such” before “studies”> Proposed change (if any): < facilitate interactions between different parties involved in such studies and may increase the.>
12	124	Comment: <Concretely, what does “adopted” mean? How does it work? What will happen in really?> Proposed change (if any): -
12	126	Comment: <“to be uniformly” does it mean mandatory?> Proposed change (if any): -
12	127	Comment: <“should be considered for implementation...” does it mean that they are optional or that they can be adapted? and In which limits?> Proposed change (if any): -
12	130	Comment:< add the word “ADVANCE” before Code of Conduct>

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		Proposed change (if any): <For each topic of the ADVANCE Code of Conduct, the text provides a definition, a list of...>
12	135	Comment: <add the word "studies" before should> Proposed change (if any): <1. Science. Benefit-risk monitoring studies should rapidly deliver the best evidence possible on the...>
12	138	Comment: idem lines 135 Proposed change (if any): < framework of benefit-risk monitoring studies should be guided by the extent to which they serve>
12	140	Comment: idem lines 135 and 138 Proposed change (if any): <3. Transparency. Benefit-risk monitoring studies should be conducted in a transparent manner, ...>
12	150	Comment: <" financial, commercial, institutional or personal interest ..." and political??> Proposed change (if any):
12	153	Comment: <1) How does this translate into actable requirements? 2) There is peer-review process but as we see in several IMI projects, it may be difficult to ensure review comments and suggestions are adequately taken into account. What about requiring that all key aspects of study design and implementation, including analysis strategy, be supported by a concise but clear and sound scientific rationale?> Proposed change (if any): -
12	156-158	Comment: <Why Pharmacoepidemiology research only? Is that realistic? When one belongs to an organization, a structure with a hierarchy and a reporting duty, how can one be guaranteed autonomy?> Proposed change (if any): -
12	159	Comment: <1) to write the full name ADVANCE Code of Conduct; 2) Do you mean that "complying with all the Code of Conduct's recommendations will safeguard the scientific independence of the research team"? The term "sufficient" can be misinterpreted, you could maybe use "basis" as follows: "those recommendations are the basis required to safeguard the scientific independence"> Proposed change (if any): <Those recommendations of the ADVANCE Code of Conduct are necessary and sufficient the basis required to safeguard the scientific independence.>
12	161-166	Comment: <1) review of some words (see in proposed change)

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		<p>2) Same thing (comment attached in line 162 to word “agreement”)</p> <p>3) Not in all situations, It depends on the level of collaboration between the parties, in case of partnership, decisions on scientific aspects will be under the responsibility of all the parties together (common decision: study design, study report publications...) (comment attached to lines 162-164)</p> <p>4) Not only a consultation in case of partnership (comment attached to lines 164-165)></p> <p>Proposed change (if any): <Clear and transparent roles and responsibilities of each party to be defined in the research contract or research agreement, providing responsibility for all decisions on scientific aspects of the study (study design, methods of data collection, data analysis, interpretation of the results, study report and publications) to the study team and allowing consultation of other parties involved in the study on important study documents such as the study protocol, study report, study analysis and manuscripts.></p>
12	167	<p>Comment: < “external experts...” in compliance with publication rules></p> <p>Proposed change (if any): -</p>
12	170	<p>Comment:< which public website? ></p> <p>Proposed change (if any): -</p>
12	171-172	<p>Comment: < How it will work? Where? When? How?></p> <p>Proposed change (if any): -</p>
12	216	<p>Comment: <Including all participants’ information></p> <p>Proposed change (if any): -</p>
12	225-227	<p>Comment: <1) When and How? What is the process? Is there something in place to collect officially these DoI?</p> <p>2) In section 4 conflict of interest></p> <p>Proposed change (if any): -</p>
12	232-233	<p>Comment: <How?></p> <p>Proposed change (if any): -</p>
12	235-236	<p>Comment: <Why are comments accessible for outside sharing but not part of basic disclosure? Maybe the protocol must include a revisions section that lists all scientific review comments and how they were addressed?></p> <p>Proposed change (if any): -</p>
12	254	<p>Comment: <Ok, but the recommendations do not specifically address this. Standard forms or declarations tend to also be biased towards financial or commercial interests...></p>

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		Proposed change (if any): -
12	262	Comment: <How can we be sure that Standard process has to be clearly defined and communicated > Proposed change (if any): -
12	301-302	Comment: < "data ownership, data access, publications and authorship" - The protocol is not the legal framework of the study, meaning that ownership, data access rights and other Intellectual property terms will be part of the research contract and not in the Protocol, in order to avoid any contradiction > Proposed change (if any): -
12	303	Comment: < "for contractual agreements between parties" - It's the scientific basis, to be part of the contract> Proposed change (if any): -
12	306-307	Comment: <Which experts, when? How? Experts without conflict of interest> Proposed change (if any): -
12	339-340	Comment: < "persons from outside the study team to provide comments" - What does it mean? If this is peer review then it should be stated out right> Proposed change (if any): -
12	375-377	Comment: <1) Not only as investigators, or which does not hold any stake in the study conduct or results. 2) How? What is the process?> Proposed change (if any): -
12	397	Comment: <In compliance with all applicable rules and regulations about publications, rules can be clearly designated maybe> Proposed change (if any): -
12	401-402	Comment: <Really mentioned in the protocol? Will be part of the contract for sure, maybe it's enough to avoid any contradiction> Proposed change (if any): -
12	403	Comment: <Independently but with prior review of the other party, who can give their comments before publication> Proposed change (if any): -
12	404	Comment: < What does "requester" mean exactly?> Proposed change (if any): -
12	406	Comment: <The other party of the agreement can have mandatory comments in some case, depends on each situation, but in collaborative way the other party can have the right to give binding comments. > Proposed change (if any): -
12	407	Comment: <How should be made public?> Proposed change (if any): -

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12	417-418	Comment: <At the beginning pf this chapter maybe in point 32> Proposed change (if any): -
12	468-469	Comment: <Is this standard process? This should be done after publication?> Proposed change (if any): -
12	471	Comment: <After publication of the study results?> Proposed change (if any): -
12	480-481	Comment: - Proposed change (if any): <Requests to for data sharing must be made on specific grounds with a justification based on the public health interest for public health, including...>
12	492	Comment: <This suggests a study team review of the protocol developed by the data sharing requestor. Is that feasible?> Proposed change (if any):-
12	493-496	Comment: < This may be a little too detailed. Maybe it only needs to state that data sharing must only be agreed upon with sufficient guarantees of data security and integrity.> Proposed change (if any):-
12	511-513	Comment: - Proposed change (if any): <The research contract may have different objectives. It will set the terms and conditions of the collaboration between the parties for the conduct of the study, which can be different depending of each study, the research contract may set out the conditions under which, for example...>
12	514	Comment: - Proposed change (if any) :< funding is provided by a party to the other party for a research project;>
12	529	Comment: - Proposed change (if any) :< Research contracts must indicate that the conduct of the studies-study will follow the..>
12	529-547	Comment: <Need to differentiate what is part of the protocol and what has to be added in the contract directly, mentioning also that the protocol will be part of the contract for the scientific aspects. Need to avoid overlap between scientific and ethical considerations in protocol and contractual/legal aspects in agreement.> Proposed change (if any):-
13	87	Comment: <suggest replacing "large" by "substantial" experience>

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		Proposed change (if any): < national and international levels based on substantial large experience and expertise.>
13	100	Comment: <suggest replacing “high” by “specific” attention> Proposed change (if any): < collaborations, and specific high attention given to actual or perceived potential conflicts of interest and...>
13	124-125	Comment: <Apparent contradiction between adoption on voluntary basis and “shall” statements, and between adoption in its entirety and lot of ‘recommendations’ mentioned as ‘should’.> Proposed change (if any): Clarify that if the CoC is used (ie, referred to), it has to be used in its entirety. Add some guidance on how one can claim (or not) that a study is conducted according to this CoC.
13	135	Comment:< Subjective – how rapid is “rapidly”?> Proposed change (if any):-
13	155-157	Comment: <1) Clarify the concept of “autonomy” of members of study team. 2) What does otherwise (line 157) mean? Are there other means than written documentation? How would this work in practice? How will ‘autonomy’ be defined?> Proposed change (if any): Make specific reference to the section in the GPP (as some organisations already comply with the GPP). Clarify the concept of autonomy of persons (scientists) within their organisations, for the conduct of the studies.
13	160-165	Comment: <In current practice, contracts (including collaborative research agreements) may only detail the activities for which the sponsor is paying and may not include full disclosure of the role of the sponsor as a participant on the study team> Proposed change (if any): <Clear and transparent roles and responsibilities defined for all parties including the sponsor in the research contract or research agreement...>
13	166	Comment: <How independent will external experts be in view of the funding that will be provided to perform the review? What about the impact on timelines in view of contracts to be put in place?> Proposed change (if any): -
13	184	Comment: <Are truthfulness and honesty not the same principle (see definition on line 189)? > Proposed change (if any):-
13	187	Comment: <1) Which functions are considered as “researchers” in a “study team”?; 2) Is evidence of this required or is this covered within the study protocol? Who will define the level of qualification needed and can this be standardized?> Proposed change (if any): Provide specific examples or list. Add a section on “Study team” (composition, roles, criteria for membership ...)

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13	189	Comment: <suggest replacing “honouring” by “fulfilling”> Proposed change (if any): <Honesty (conveying information truthfully and fulfilling honouring commitments)>
13	194	Comment: <suggest replacing “validity” by “reliability”> Proposed change (if any): < The study team is responsible and accountable for the integrity and reliability validity of its work.>
13	225	Comment: <not clear where the DoIs will be posted; Clarify whether DoIs should be “documented” and/or “disclosed”?. Proposed change (if any):-
13	231	Comment: <start paragraph with “after completion of final study report”> Proposed change (if any): < After completion of final study report, study information should be made available to researchers from outside the study team in an..>
13	240	Comment: - Proposed change (if any): add that subjects entitled to receive lay summary of study results
13	259-260	Comment: <1) How would this (management of CoI) is done practically, for example if a study team includes member of a vaccine manufacturing company?; 2) Who will decide (how) that the potential conflict of interest is acceptable?> Proposed change (if any):-
13	274/Study protocol section	Comment: <nothing on Consent> Proposed change (if any): -
13	274-276	Comment: < Does it really mean ALL details should be incorporated in the protocol? Full procedural details?> Proposed change (if any): <Document containing all the technical methodological details of the design, implementation, key analytical aspects (In line with line 319), documentation and publication of the results of an epidemiological study, including planned timelines.>
13	283	Comment: <suggest replacing “need” by “rationale”> Proposed change (if any): <... the rationale need for the study – that is, why the study should be conducted, given the current...>
13	290-291	Comment: ,In practice, how should the ability, skill of conduct and design knowledge is documented IN the protocol besides a CV in appendix and a signature of the protocol?> Proposed change (if any): -
13	292-293	Comment: - Proposed change (if any): < the provisions made to protect participants' personal data and meeting legal and regulatory requirements >.
13	301-303	Comment: <This may be difficult to apply in practice as it may be necessary to include protocol development as a deliverable in the contract. In such cases, the protocol will not be finalised prior to contracting.

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		"Description of the contribution of each party to the study design, writing of protocol and the study work programme" → This will be redundant with the contract and is usually not mentioned in the protocols.> Proposed change (if any): -
13	306-308	Comment: <1) Is there a recommended means for making such comments public? They would not normally be included in any of the public study registers; 2) In general are such reviews made public at present? If not, should this be extended to suggest means of publicising? 3) "study work programme with information on timelines, data ownership, data access, publications and authorship" → This is usually not in the protocol as variable but in the legal agreement appendix> Proposed change (if any): -
13	307	Comment: <Where will the recommendations be made public?> Proposed change (if any): -
13	309	Comment: <how can independency be guaranteed? All study types or only very complex/specific safety studies?> Proposed change (if any): -
13	312	Comment: - Proposed change (if any): <...auditable way including the dates of the changes and rationale for change>
13	314-315	Comment: - Proposed change (if any): suggest moving to Transparency section
13	325-326	Comment: - Proposed change (if any): ...including interim analysis if any
13	366	Comment: Proposed change (if any): Sources affecting data quality and strengths and limitations of the study must be described.
13	375-378	Comment: <As above. Through what means of disclosure? Rapidly: use regulatory requested timelines?> Proposed change (if any): -
13	382-384	Comment: <What's the purpose of this review? Is it needed (as long as we have capable/honest researchers)> Proposed change (if any): -
13	400-403	Comment:< Not clear what is meant by publication "policy". Not clear what should be described in the protocol as opposed to the contract(s).> Proposed change (if any): Refer to publication "plan" instead and list specific components of the plan (authorship, journals, timelines ...)
13	407	Comment: <Through what means?> Proposed change (if any): -

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13	419-420	Comment: <For all studies? Is this a request from authorities/PHA besides mandatory studies that manufacturers have in their RMP? Who should set up these procedures?> Proposed change (if any): -
13	464	Comment: <Any recommendation here on length of retention period for study data?> Proposed change (if any): -
13	478	Comment: - Proposed change (if any): replace “should” by “must”
13	492-493	Comment: <Should requests for sharing of data and the top level reasons in deciding whether to allow sharing be made publicly available? To avoid accusations of acting in self rather than public interest.> Proposed change (if any): -
13	494-497	Comment:;, Should some advice on appropriate consenting of patients so that appropriate data sharing will be possible without losing subjects for the original study be given in the preceding section?> Proposed change (if any): -
13	534	Comment: <The protocol is appended to the contract; study details are usually not mentioned in the core text of the contract.> Proposed change (if any): -
14	84	Comment:;, Which public does it refer to? Is it open to all vaccines companies, health authorities, learned societies, patient organizations. In order to improve acceptability, all of these should be proactively approached.> Proposed change (if any): -
14	120-123	Comment: - Proposed change (if any): <These principles will also facilitate interactions between different parties involved in studies and aims at may increase increasing the confidence of health professionals and the public about the quality of their results. The ADVANCE Code of Conduct applies to all individuals and organisations participating in to such studies.>
14	124-125	Comment: - Proposed change (if any): < The ADVANCE Code of Conduct should be followed in its entirety be adopted voluntarily by all parties involved in a study and it should be adopted entirely. >
14	132 (section B)	Comment: <to revert point 1 and 2, Public health becomes 1 (also to replace “serve improving” with “help to improve”) and Science become 2 > Proposed change (if any): <1. Public Health. All decisions on the prioritisation, conduct and communication to be taken in the framework of benefit-risk monitoring should be guided by the extent to which they help to improve serve improving the health of individuals and the population.

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		2. Science. Benefit-risk monitoring should rapidly deliver the best evidence possible on the research question, applying the appropriate scientific methods with integrity.>
14	149	Comment: - Proposed change (if any): < financial, commercial, institutional or personal interest in the conduct or a particular outcome of the research.>
14	152	Comment: <i>undue influence</i> - the entire term is very important. Proposed change (if any): -
14	153	Comment: - Proposed change (if any): < of any financial, commercial, institutional or personal interest in the conduct or a particular outcome of the ...>
14	155-157 (rec 2)	Comment: <recommendation 2 to become recommendation 3> Proposed change (if any):
14	174	Comment: < <i>EFPIA Code on the Promotion</i> - very good> Proposed change (if any): -
14	184	Comment: <Scientific integrity means is acting in accordance with the values of science, such as truthfulness, honesty> Proposed change (if any): -
14	187	Comment: <How is this defined? What does qualification entail? How many years of experience until someone is "experienced"?> Proposed change (if any): -
14	189-190	Comment: <Very important, fundamental principles that need to be reminded each time, although it's a challenge to measure and/or document. We need to rely on compliance implementation...> Proposed change (if any):-
14	194-195	Comment: - Proposed change (if any): < The study team must should adhere to Good epidemiological practices and Good ...>
14	224-225	Comment: < <i>the members of the study team and external advisory committee</i> – 1) We should also insert "objective selection criteria for study investigators and experts", pursuant to recommendations 5 and 6, above; 2) These terms need to be defined.> Proposed change (if any):
14	225-226	Comment: - Proposed change (if any): < Potential conflicts of interests must be declared and remediated in the study report and in publications.>

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14	253-254	Comment: <1) <i>personal or familial relationship</i> - Very good; 2) <i>beliefs</i> - No - this appears to be either a discrimination or prejudicial (judgement based on what one believes the intention of the other is). All researchers have their beliefs: philosophical, moral or religious (which turn into scientific). This is perfectly ok as long as these beliefs can be objectivized, substantiated, etc.> Proposed change (if any): -
14	256	Comment: - Proposed change (if any): <Actual or potential conflicts of interest must be identified and remediate addressed at the planning phase
14	261	Comment: < <i>standard form</i> - Who is developing it?> Proposed change (if any):
14	261-263	Comment: <Add a provision stating that unresolved conflict of interests leads to the exclusion of the conflicted participant in the interest of the credibility and objectivity of the research project.> Proposed change (if any): -
14	293-294	Comment: Proposed change (if any): <Internationally-agreed guidelines should be consulted to ensure that the protocol covers all important aspects of the protocol have been covered >
14	295-297	Comment: <Suggestion to add also to this list the "Pharmacovigilance requirements"> Proposed change (if any): -
14	305	Comment: - Proposed change (if any): < A detailed draft protocol must should undergo independent scientific review by experts that did not >
14	403-404	Comment: - Proposed change (if any): <The requester/funder must should be entitled to view the results and interpretations included...>
14	446-447	Comment: <Perhaps we could add a little more substance with regard to the principles of necessity of processing data, the right to request the data to be deleted etc. as well as potentially the significant penalties that are planned under the EU Regulation.> Proposed change (if any): -
14	474	Comment: - Proposed change (if any): < It is the responsibility of the principal principle investigator >
14	491	Comment: - Proposed change (if any): < scientific quality of the protocol are must be important elements to be considered for the decision.>
15	71	Comment: -

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		Proposed change (if any): < The Accelerated Development of VAccine beNefit-risk benefit-risk Collaboration in Europe (ADVANCE)...>
15	73	Comment: <"vaccine benefits and risks in Europe" does this only include "observational studies" as line 120 states?> Proposed change (if any): -
15	85-86	Comment: <Various guidelines for conducting epidemiology studies are mentioned but the actual references are not provided. In addition, it is stated that various guidelines, as well as articles identified from a literature review, were analysed and used as a starting point for the development of the ADVANCE code of conduct. However, the results of the analyses are not presented. It appears that the "gap analysis" was conducted which led to the need for ADVANCE CoC. However, the findings from this gap analysis are not sufficiently synthesized and/or highlighted. > Proposed change (if any): Provide references for all guidelines / publications that were accessed and evaluated and present the summary of those findings
15	92-94	Comment: <It is stated that none of the existing guidelines fulfilled all the needs of the post-authorisation benefit-risk monitoring of vaccines or could be used as a stand-alone reference to ADVANCE. This statement is not sufficiently supported. While examples are presented as to how vaccines are different from medicinal products, these examples do not in themselves explain the need for additional considerations.> Proposed change (if any): Provide further evidence as to why the existing guidelines are not sufficient. There are numerous considerations when it comes to formulating research question, writing a protocol, etc that should not be different for vaccines studies. Consider highlighting sections that can be equally applied to vaccine studies as they apply for medicinal products studies and those that need to be specifically modified for the purpose of vaccine work which is rooted in public health and disease prevention where large populations, typically healthy infants and children (i.e., the most vulnerable) get vaccinated and the impact these vaccinations may have.
15	112	Comment: <I believe the proposed code of conduct will slow down the evaluation of the benefits and risks of marketed vaccines. The values Science, Public Health, and Transparency are all good things, but that does not mean the process will be faster. > Proposed change (if any): -
15	113	Comment: <1) I suggest that a section of scope be added. Even though we can find it in the sentences, it would be better that reader can easily find it and clearly check if a study should follow this document; 2) The scope of work which would necessitate following ADVANCE CoC is not provided > Proposed change (if any): Include the scope of work. Similar to the Guidelines for GPP by ISPE state: "The GPP are intended to apply broadly to all types of pharmacoepidemiologic research, including feasibility studies, validation studies, descriptive studies,

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		as well as etiologic investigations, and all of their related activities from design through publication...” Relevant text specific to vaccines work can then be developed
15	118-119	<p>Comment: <It is stated that the ADVANCE Code of Conduct is primarily intended for studies with collaborations or partnerships between different organisations but it may also be used for other types of studies, such as self-supported studies or studies supported by grants. However, no definition or explanation of two terms, “organizations” and “self-supported” studies are provided. These are seemingly common terms that may be interpreted differently by different stakeholders.></p> <p>Proposed change (if any): Provide definitions and/or relevant examples to explain what is meant by organizations and self-supported studies.</p>
15	120	<p>Comment: <“observational studies” Good to be consistent with line 73, studies on “vaccine benefits and risks in Europe”.></p> <p>Proposed change (if any): -</p>
15	121	<p>Comment: <change ‘facilitate’ to ‘increase’, because I think the recommendations require more interactions, which will not make the interactions faster. .</p> <p>Proposed change (if any): < increase facilitate interactions between different parties involved in studies and may increase the...></p>
15	122	<p>Comment: <change ‘their results’ to ‘study results’.></p> <p>Proposed change (if any): <confidence of health professionals and the public about the quality of study results their results. ></p>
15	123	<p>Comment: change ‘participating to such’ to ‘participating in such’.</p> <p>Proposed change (if any): <Code of Conduct applies to all individuals and organisations participating in to such studies.></p>
15	137	<p>Comment:;, One of the values highlighted is public health. “All decisions on the prioritisation, conduct and communication to be taken in the framework of benefit-risk monitoring should be guided by the extent to which they serve improving the health of individuals and the population.” As this sentence is formulated it is unclear which decisions are referenced here and what is meant by prioritization.></p> <p>Proposed change (if any): Reformulate the text that discusses public health value.</p>
15	146	<p>Comment: <change ‘is the situation where’ to ‘means’></p> <p>Proposed change (if any): <Scientific independence is means the situation where all decisions on scientific aspects of the research...></p>
15	151	<p>Comment: <Government officials can never be independent if they report to a political institution like the MoH, which may have strong financial and political interests in the outcome of a study. Additional CoI arise e.g. if building a factory, tech transfer etc. are considered. ... Government workers reporting to MoH should identify the reporting line. Having said this, GO with a reporting line to the MoH cannot be part in a study team.></p>

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		Proposed change (if any): -
15	154	Comment: <I would also include the reporting lines here for GOs.> Proposed change (if any): -
15	151-154	Comment: <It will be important to understand what this means. In assessing Benefit:Risk, outcomes research with financial endpoints will be very important in determining the value of a vaccine as a public health intervention. It is valuable to have individuals skilled in outcomes research and financial modelling as a part of the process.> Proposed change (if any): it would be good to emphasize that economic studies are included or excluded.
15	155-157	Comment: <documenting autonomy of study team members sounds like a requirement for another form> Proposed change (if any): -
15	172	Comment: <Disclosure to whom and where?> Proposed change (if any): -
15	187-194	Comment: <Recommendation numbers 5,6 & 7 on page 6 should be 4,5 & 6.> Proposed change (if any): -
15	185	Comment: <delete 'even when no one is looking over the researcher's shoulder', because integrity is integrity.> Proposed change (if any): <...and open reporting. even when no one is looking over the researcher's shoulder >
15	187	Comment: <1) "open reporting, even when no one is looking over the researcher's shoulder" could be openness and objectiveness; 2) It is stated that all researchers involved in the study team must be qualified and experienced scientists. It is unclear what is meant by qualified and experienced; 3) Question whether all people in study team need to be experienced and whether it would be sufficient to qualified. Otherwise could be issue to have new hires and new graduates in teams. Also, how will qualification be determined? If only experienced scientists can work on these studies, how will we ever get new people with experience?> Proposed change (if any): 1)- 2) Consider adapting the text from Guidelines for GPP by ISPE Original text in Guidelines for GPP by ISPE states: "Personnel engaged in epidemiologic research and related activities should have the education, training, or experience necessary to perform the assigned functions competently.

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		Modified text for ADVANCE CoC: Personnel engaged in benefit risk monitoring/assessment of vaccines should have the educations, training or experience necessary to perform the assigned functions competently 3) remove 'and experienced' 4) change 'experienced scientists' to 'experienced' because not all researchers need be scientists
15	198	Comment: <Not sure we need to use the word transparent in every section of the code.> Proposed change (if any): -
15	217	Comment: <change 'Every study related to the monitoring of the benefit-risk of vaccines' to 'Every study related to the determination of the benefit-risk of any vaccine or vaccines'.> Proposed change (if any): < Every study related to the determination monitoring of the benefit-risk of any vaccines or vaccines must be registered in a ...>
15	218	Comment: <for the requirement to register every study before the start of data collection or data extraction, suggest change it to 'before the start of data collection for a prospective study, or data extraction for retrospective study'.> Proposed change (if any): -
15	219	Comment: <Change 'study protocol providing' to 'study protocol and provide'.> Proposed change (if any): <registration should include the study protocol and provide providing enough information to understand and...>
15	227	Comment: <1) Do we mean to load full study report? This may pose a significant burden on the study team, therefore delay the time when public can have access to main results. Suggest to change it to ' study report with primary conclusions and key findings'; 2) Making public of all detailed information would lead to a misuse or wrong interpretation of specific data. Suggest to disclose only key findings and summary.> Proposed change (if any): -
15	229	Comment: <Recommendations from the external advisory committee must be made available to 'all participants'. Does 'participants' include subjects in the study?> Proposed change (if any): -
15	231-232	Comment:< when recommendations will be available for all participants and by which way/format to participants?> Proposed change (if any): -

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15	231-236	<p>Comment: <1) In the section “transparency,” it is stated that the study information should be made available to researchers from outside the study team in an open and collaborative approach. However, it is unclear what the term “researchers” encompasses/represents. For example, does it imply that all work associated with benefit risk studies of vaccines conducted by ADVANCE will be publically available and anyone could in theory request a copy of programming codes?</p> <p>2) Maybe not. Some of these have potential to be proprietary. Data sets could potentially be made available as they are to regulatory authorities. As I recall, we currently have evolving policy on making data available to investigators on a case by case basis, based on quality of science, internal adjudication, and external independent review (if rejected internally.) It appears that written request is included here, but an adjudication process would be required.</p> <p>Scientific comments would need to be redacted if they included proprietary info from a regulatory document.></p> <p>Proposed change (if any): Clarify the circumstances under which information will be made available outside of the team and what this information will include.</p>
15	237-238	<p>Comment: <This is something now baked in to our current reporting expectations. However, it is critically important that subjects are provided an unbiased interpretation of results, rather than merely a “data dump”.></p> <p>Proposed change (if any): -</p>
15	238	<p>Comment: <1) subjects who participate in study are entitled to receive the main study results. So if data is collected thousands of subjects in a registry, is each subject entitled to receive the main study results? If so, who is responsible for notifying the subjects? Who would pay for distribution costs? ;</p> <p>2) Won't the study results be posted to site mentioned in point 7? If so, why can't the participants access the main study results there? Of course the subjects should be entitled to see their own data.></p> <p>Proposed change (if any): -</p>
15	239-240	<p>Comment: <The study results will be published in a public website. We might not need to specify this again here. ></p> <p>Proposed change (if any): -</p>
15	258	<p>Comment: <Delete ‘Perceptions of conflicts of interest are as important to be addressed as actual or potential ones’ because managing perceptions of conflicts of interest will be almost impossible. ></p> <p>Proposed change (if any):</p>
15	263	<p>Comment: <DoIs must be updated ‘immediately’ in case of a change. 1) So if study statistician resigns from study, and new statistician is hired, then it sounds like everybody’s DoI must be updated. Correct?</p>

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		2) How soon is 'immediately'? 1 day? 1 month? >
		Proposed change (if any): -
15	273	Comment: <What do we mean by timeline here? Do we mean timeframe for data collection as part of study design, or do we mean study conduct timeline? Suggest to clarify it.> Proposed change (if any): -
15	274	Comment: <"The study protocol includes all the procedures developed or used": This sounds like assay methodology must be described, in detail, in the study protocol. > Proposed change (if any): -
15	276	Comment: <"study protocol includes all ... and any changes..." I think protocol amendment includes all changes not initial protocol.> Proposed change (if any): to rephrase sentence to include protocol amendment
15	282-283	Comment: <change 'may have not been relevant or feasible' to 'are judged not relevant'.> Proposed change (if any): <...methodological choices and why some of the possible options are judged not relevant may have not been relevant or feasible >
15	283-285	Comment: <Do we talk about primary hypothesis or all hypotheses? There would be plenty or no alternative options to address all hypotheses in the protocol. It may be not applicable to explain why some of possible options are not feasible as there could be no alternative. I think explain the rationale or appropriateness of choice of analysis method would be sufficient. If we do want discuss inappropriateness of some analysis method, I suggest discussing the primary hypothesis only. > Proposed change (if any): -
15	287	Comment: <Investigators should be aware of all limitations in the design. How would the protocol demonstrate that the investigator(s) are 'aware of all limitations in the design'? - would the protocol have to include copies of appropriately signed forms?> Proposed change (if any): -
15	289	Comment:< change 'covering' to 'with'.> Proposed change (if any): <The study protocol must be developed by a team of persons with covering relevant expertise>

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15	291	Comment: <1) Sounds like study team must include an ethicist; 2) "The process for reaching an agreement on design options should be agreed beforehand between the different persons involved": This sounds like the process for 'reaching an agreement on design options' must be completed before starting the protocol. > Proposed change (if any): -
15	295-296	Comment: <Design options should be agreed beforehand between " the different persons involved" Who are those different persons can finalize the design? Shall we more specific about different persons involved or can we say by the study team?> Proposed change (if any): -
15	300	Comment: <Please define 'study work programme'.> Proposed change (if any): -
15	301-302	Comment:< The word "used" is used to much> Proposed change (if any): -
15	304	Comment: <1) 'with a rationale' – rationale for what?; 2) remove the second period> Proposed change (if any): -
15	305	Comment: <Regarding requiring <u>draft</u> protocol to undergo independent review: I predict that this will slow protocol development, because of the time needed to circulate and collect comments from external experts> Proposed change (if any): -
15	308	Comment: <Isn't this already covered in transparency section?> Proposed change (if any): -
15	308-309	Comment: <Operationally it is not doable for retrospective study. Suggest change 'before the start of data collection' to 'before the start of data collection of a prospective study or data extraction for a retrospective study'> Proposed change (if any): -
15	319	Comment: <Suggest that for database studies, description of data source, data elements, advantage and limitation be provided. > Proposed change (if any): -
15	331	Comment: < I suggest that the document provide guidance of adverse event reporting. For instance, when it is s a database study, adverse event reporting may not be applicable since the databases are usually anonymized.>

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		Proposed change (if any): -
15	324	<p>Comment: < Analysis plan should be finalised before ... "extraction". Shall we change to "first data extraction for (interim) analysis"?></p> <p>Proposed change (if any): -</p>
15	335	<p>Comment: <It seems we also discussed a lot about analysis in this section, shall we change the subsection title to "Study Analysis and Report".></p> <p>Proposed change (if any):</p>
15	337	<p>Comment: <"There must be a plan for responsibilities as regards to the study report . . . "sounds like a longer protocol is required, ie, more time to develop a protocol.></p> <p>Proposed change (if any): -</p>
15	343-344	<p>Comment: <1) It might be difficult to identify specific persons rather than outside party in the plan. A separate plan outside protocol might be easily managed; 2) delete 'in line with the provisions'.></p> <p>Proposed change (if any): <...reasonable scientific explanation should be provided in line with the provisions for changes></p>
15	345	<p>Comment: <change 'ones' to 'results'.></p> <p>Proposed change (if any): < results ones must always be presented as such.></p>
15	351	<p>Comment: <Items listed here should be considered during the development of protocol and SAP. Some of them (modifying the study population, unmeasured confounders, etc.) are not addressable after the study is done, as the information is not available by then.></p> <p>Proposed change (if any): -</p>
15	356	<p>Comment: <Should add "as appropriate" to end of the sentence.></p> <p>Proposed change (if any): <association between the a priori exposure of interest and the outcome(s) as appropriate.></p>
15	361-363	<p>Comment: <1) I believe that this can be incorporated in the SAP instead of a separate plan; 2) "secondary data" term should be defined></p> <p>Proposed change (if any): -</p>

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15	364	Comment: < Who is a secondary user? National health authority? Other researchers? Please define.> Proposed change (if any): -
15	368	Comment: <Please define 'data custodian'.> Proposed change (if any): -
15	378-380	Comment: <regarding independent review of draft study report, I expect this means nondisclosure agreements will have to be drafted, approved, and signed. Also longer timelines as draft is circulated among very busy experts. > Proposed change (if any): -
15	374-377	Comment: <If published, a formal procedure/form/process is needed. It is not very clear to me.> Proposed change (if any): -
15	396	Comment: <delete 'Presentations at meetings are not substitutes for publications in peer reviewed literature' because it is not enforceable. I agree that presentations at meetings would not be a substitute, but team only has to 'attempt' to publish. > Proposed change (if any): -
15	397-399	Comment: <Repeat of lines 377-378.> Proposed change (if any): -
15	400-401	Comment: <If publication policy will be in the research contract, it would not be advisable to have a copy in the protocol. > Proposed change (if any): -
15	405-406	Comment: <This is new I think. Internal correspondence between investigators and sponsors is not typically public. Not sure how this would work, or whether it would only pertain to disagreements about content.> Proposed change (if any): -
15	408	Comment: <regarding "In no circumstances should the results be changed": what if gross error found in analysis program? If the study results are reported in error, they should be updated. It is dangerous to use qualifiers like "in no circumstances" > Proposed change (if any): -
15	409	Comment: <Who defines 'urgent'? > Proposed change (if any): -

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15	410	Comment: <requiring independent peer review of results means nondisclosure contracts needed. Also delay in releasing results. > Proposed change (if any):
15	414	Comment: <I assume informing regulatory and public health authorities of results comes after independent review, so the document should say so. > Proposed change (if any): -
15	462	Comment: <Under section 9: sharing if study data, we have recommendations on how study team share data with outside the study team. Wish to see some recommendations on sharing the analysis/results/interpretations done by the outside requester.> Proposed change (if any): -
15	473	Comment: <delete 'normally'.> Proposed change (if any): -
15	474-478	Comment: <This is where an independent adjudication committee would be useful, in circumstances where request is rejected due to lack of scientific merit, bias, or other reason.> Proposed change (if any): -
15	479	Comment: <Change 'Requests to data sharing' to 'Requests for data sharing'.> Proposed change (if any): < Requests for data sharing must be made on specific grounds with a justification based on the >
15	491	Comment: <delete 'important elements to be'> Proposed change (if any): -
15	496-497	Comment: < Can other option(s) be considered, such as CD?> Proposed change (if any): -
15	523	Comment: <delete 'unique'.> Proposed change (if any): -
15	525	Comment: <change 'established for a same study' to 'established for the same study'> Proposed change (if any): < bipartite contracts need to be established for a same study, the terms of agreement should be >
15	527-530	Comment:< This is very important when programming and Stat parties are not in the same CRO. > Proposed change (if any): -
15	538	Comment: <Can this be included in the CSR writing plan?> Proposed change (if any): -
17	149	Comment: <conflict may also come from political interests> Proposed change (if any): <without undue influence of any financial, commercial, political, institutional or personal interest>

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17	160	<p>Comment: <the independence of the organizations involved in the study must be granted through a transparent process of recruitment, where the ultimate choice does not rely solely in the hands of the sponsor, SEE GENERAL COMMENT ABOVE></p> <p>Proposed change (if any): Transparent process for choosing the organisations involved in the study, for instance via a public tender or (in case of time constraints) a motivated choice among a public list of research organisations; the choice must be aimed to select organisations that guarantee scientific independence</p>
17	171	<p>Comment: <1) The commitment to publish the results of the study independently on the outcome can be anticipated in this section; 2) The scientific community should be given a chance to replicate the analysis on the analytical dataset></p> <p>Proposed change (if any): 1) Commitment to publish the results whatever they are; 2) Commitment to make the analytical dataset available to the scientific community for further analyses or re-analysis, unless legal constraints prevent from doing so, in which case the provisions of section 9 should hold.</p>
17	187	<p>Comment: <Young researchers should have a chance to participate in the study groups></p> <p>Proposed change (if any): <All researchers involved in the study team must be qualified scientists, and the study leaders must be experienced scientists.></p>
17	199	<p>Comment:< the scientific decision process should be accountable. To add recommendation 8, as in the proposed change></p> <p>Proposed change (if any): <8. In case of conflict internal to the study team, a transparent decision making process should be put in place. Minutes of the relevant meetings (in which key decisions are taken on study design, methods of data collection, data analysis, interpretation of the results, study report and publications) should be made publicly available, in which minority positions should be documented.></p>
17	215	<p>Comment: -</p> <p>Proposed change (if any): < Transparency is having comprehensive study information accessible to all.></p>
17	226	<p>Comment: <To ensure that interests are not prevalent in the conduct of the study they should be not only declared but also balanced within the study team></p>

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		Proposed change (if any): to add < ..., and in particular any potential financial, commercial, political, institutional or personal interest in a particular outcome of the research. The composition of the study team and of the external advisory committee should be balanced with respect to the interests represented.>
17	238	<p>Comment: <In the case of epidemiologic studies transparency should prevail over confidentiality. The agreements between parties should be disclosed; to add recommendation 14 , as in the proposed change></p> <p>Proposed change (if any): <14. No confidentiality or secrecy agreement/contract having as object the content of the study should be sought between the involved parties. The existence of any other confidentiality or secrecy agreements or contracts among any of the parties involved in the study should be disclosed, and the content of such agreements should be auditable by trusted third parties.></p>
17	254	<p>Comment: <Interests of organizations, not only of individuals, are very relevant. They should be disclosed clearly as well. SEE GENERAL COMMENT ABOVE></p> <p>Proposed change (if any): to add paragraph <Professional interest may occur because of any financial, commercial, political interest of the organisation that employs the person towards a particular outcome of the research.></p>
17	263	<p>Comment: <The previous recommended change must be embedded in a specific recommendation, SEE ALSO THE GENERAL COMMENT ABOVE; to add recommendation 16, as in the proposed change></p> <p>Proposed change (if any): <16. The potential conflict of interest of the organisations involved in the study must be declared separately, in a standard form.></p>
17	280	<p>Comment: <Studies should not be conducted if the literature already supports in a solid manner a statement></p> <p>Proposed change (if any): to add <..., state of knowledge, as assessed by a systematic literature review></p>
17	320	<p>Comment: <A time framework should be specified for development of detailed statistical plan></p> <p>Proposed change (if any): <Key statistical analyses should be described in the study protocol. A detailed statistical analysis plan should be finalised before or soon after the start the end of data collection or extraction.></p>
17	340	Comment: <Responsibility for data management should be clarified, but the study team must be enabled to perform data analysis; to add recommendation 26 , as in the proposed change>

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		Proposed change (if any): < 26. The study team should decide who will be the custodian of the analytical dataset, who will be in charge of putting into place appropriate procedures for preserving data security and privacy. All members of the study team should have unrestricted access to the analytical dataset.>
17	478	<p>Comment: < If the scientific community wants to replicate the analysis on the analytical dataset, this should be made possible as a general rule. Exceptions should be justified.></p> <p>Proposed change (if any): to add <As a general rule, permission to access the analytical dataset should be granted, to research team members on the basis of a solid grounded request ></p>
17	526	<p>Comment: <For transparency the obligations among partners should be public; to add recommendation 50, as in the proposed change></p> <p>Proposed change (if any): <50. Research contracts should be publicly accessible></p>
18	73	<p>Comment: <understandably specific to vaccines, but principles have wider application ></p> <p>Proposed change (if any): -</p>
18	78	<p>Comment: <Potentially all such studies would be along the product lifecycle for vaccines and for other therapeutic compounds/products></p> <p>Proposed change (if any): -</p>
18	83	<p>Comment: <within a wider context of e.g. pharmaceuticals? ></p> <p>Proposed change (if any): -</p>
18	101	<p>Comment: <an opportunity exists also to harmonise such guidelines within Europe, reducing complexity for all stakeholders></p> <p>Proposed change (if any): -</p>
18	125	<p>Comment: <what if the Code is not adopted, are there penalties or sanctions? ></p> <p>Proposed change (if any): -</p>
18	136	<p>Comment: <would that not also include e.g. Good Clinical Practice (GCP)?></p> <p>Proposed change (if any):</p>
18	139	<p>Comment: <how is the extent of improvement measured or evaluated?></p> <p>Proposed change (if any): -</p>
18	149	<p>Comment: <and this needs to be open to audit></p> <p>Proposed change (if any): -</p>

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18	157	Comment: <guaranteed by all parties> Proposed change (if any): -
18	169	Comment: <should be a <i>relevant</i> website > Proposed change (if any): -
18	171	Comment: <should be open to audit > Proposed change (if any): to add <... declaration of interest should be provided by all organisations involved in the study >
18	196	Comment: <would that not also include e.g. GCP?> Proposed change (if any): -
18	223	Comment: <likely also included/recorded within the database in item 7> Proposed change (if any): -
18	228	Comment: <within a given time period to be defined? (e.g. 6 or 12 months); failure to comply with this commitment should be justified and a new deadline should be submitted > Proposed change (if any): -
18	256	Comment: <how will this be addressed to avoid the influence of conflict of interest?> Proposed change (if any): -
18	365	Comment: <within their <i>own</i> data> Proposed change (if any): -
18	378	Comment: <within a given time period to be defined? (e.g. 6 or 12 months); failure to comply with this commitment should be justified and a new deadline should be submitted> Proposed change (if any): -
18	399	Comment: <within a given time period to be defined? (e.g. 6 or 12 months); failure to comply with this commitment should be justified and a new deadline should be submitted> Proposed change (if any): -
18	410	Comment: <even for urgent public health issues there are mechanisms for rapid peer review (e.g. as seen recently for Ebola)?> Proposed change (if any): -
18	429	Comment: <there appears to no reference to subject consent and the re(use) of health data, either to linked to subject privacy, or in general terms for health research, which appears to be a marked omission. It would be good to see a statement regarding the assurance of patient consent where appropriate for re(use) of health data.> Proposed change (if any): -
18	495	Comment: <this is also subject to appropriate legal/regulatory requirements by institute, local and regional (EU) requirements.> Proposed change (if any): -

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19	247	<p>Comment: <The section 4, which is on conflicts of interests, is a bit vague. It is not clear how matters such as 'academic conflicts' or beliefs to be dealt with when addressing conflicts of interests.></p> <p>Proposed change (if any): -</p>
19	308-309	<p>Comment: <Recommendation 22 could be moved from 'must' to 'should' as it might not be possible to register study protocol in all countries and settings and it should not be a limiting factor in initiation of the research work.></p> <p>Proposed change (if any): -</p>
19	527-545	<p>Comment: <Not sure if the recommendation 50 should be retained. The ADVANCE should be the guiding principle and not a must thing. ></p> <p>Proposed change (if any): -</p>
20	(not all lines to which this applies have been specified with this comment)	<p>Comment: <The CoC suggests a summary report would be acceptable, but this is not consistent throughout. ></p> <p>Proposed change (if any): Change to posting of summary report throughout.</p>
20	67	<p>Comment: < (see also General comments) General concern that posting of comments at the draft protocol stage may not be feasible and may impact the openness of the comments due to concern of public perception of the reviewers. ></p> <p>Proposed change (if any): Careful consideration should be given to the level of detail, timing, efforts and purpose of public disclosure of external advisor comments. Alternatively, consideration should be given to disclosure of information at the time of the report, rather than at time of the study protocol, or upon request.</p>
20	70 (, not all lines to which this applies have been specified	<p>Comment: <It should be possible to post a redacted protocol to avoid any potential selection or information bias and without potential market competitive information. Protocol posting is mentioned multiple times throughout the document.></p>

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	with this comment).	Proposed change (if any): change to "(Redacted) Protocol posting on public website before study data collection or extraction.
20	125	<p>Comment: <The COC states "The ADVANCE Code of Conduct should be adopted voluntarily by all parties involved in a study and it should be adopted entirely".></p> <p>Proposed change (if any): Add: <... and providing that it is compliant with (local) law/regulation. ></p> <p>Certain sensitive or emergency situations may require to deviate from the COC principles.</p>
20	231	<p>Comment: <Clarify whether the term "participants" in this sentence refers to study subjects or members of the research team. ></p> <p>"Recommendations from the external advisory committee or peer reviewers must be made available to all "participants" (?) in the study, including the study requester and study funder".</p> <p>Proposed change (if any):-</p>
20	165 and 237	<p>Comment: <The CoC states</p> <p>"with disclosure of all comments from any party to all those parties involved in the study"</p> <p>"...and all scientific comments received on key study documents"</p> <p>There is concern of the feasibility to achieve this level of disclosure. Does this also mean the comments from the study team members on every draft, or those received from a formal protocol review committee? Practical/feasibility considerations should be taken into account. Please see also general comments for other considerations of public disclosure.></p> <p>Proposed change (if any): -</p>
20	261	<p>Comment: <The CoC indicates that the research contract <u>must</u> have a clear description of the management of conflicts of interest. ></p>

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		Proposed change (if any): Is adherence to principles and measures the CoC in itself not intended as to provide sufficient and appropriate measures to manage conflict of interest?
20	263	<p>Comment: <Declarations of Interests (DoI) are generally not published upfront but published at time of the report or as part of the report. (for example in the case of experts assigned by WHO advisory committees)></p> <p>Proposed change (if any): Declarations of interest should be gathered before (or during in case of updates), but can be published after/with or as part of the report.</p>
20	267	<p>Comment: <the CoC states that: "The study protocol includes all the procedures developed or used during the study and any changes made to the initial protocol."</p> <p>This should balance with consideration for what is the necessary to interpret the data and the quality.></p> <p>Proposed change (if any): -</p>
20	287	<p>Comment: <The Coc states that: "<i>the feasibility of doing the study as proposed - that is, that the study can be completed successfully in the specified time and with the available resources;</i>"</p> <p>Generally, resource management is not part of the protocol, but part of the contract. Consideration should be given to the purpose/function of the protocol and that of the contract without unnecessary duplication of content.></p> <p>Proposed change (if any): -</p>
20	301-303	<p>Comment: <Roles and responsibilities are generally described in detail in a research contract, but not the protocol. ></p> <p>Proposed change (if any): Consideration should be given to the purpose/function of the protocol and that of the contract without unnecessary duplication of content and risk of discrepancies between study documents.</p>
20	303	<p>Comment: Authorship is generally not decided upfront, but determined retrospectively on the basis of the contributions.</p> <p>Proposed change (if any): Policy for determining authorship could be defined, but not the actual authorship.</p>

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20	303-304	<p>Comment: <The CoC specified that the protocol should be used as the reference document to be used as the basis for contractual agreements between parties. However, this does not consider the situation that the protocol is often drafted as part of the contractual agreement, which would then lead to circular reasoning.></p> <p>Proposed change (if any): -</p>
20	305	<p>Comment: <Specify that the protocol can reference applicable guidances/requirements, but not necessarily should incorporate/specify all. ></p> <p>Proposed change (if any): A specific section should <u>reference</u> the regulatory obligations and recommendations applicable to the study, with a rationale.</p>
20	346	<p>Comment: <the CoC states "Outcomes resulting from changes to the analysis plan after data analysis has begun, e.g. formation of new sub-groups based on knowledge of (initial) study results, that must not be used for the purpose of verifying or rejecting the primary hypotheses stated in the protocol but can be used to generate further hypotheses."</p> <p>It not clear how this should be interpreted. For example, if in the results a confounding factor has an unforeseen effect, additional analysis could be performed, but if that then leads to rejection the primary hypothesis then this could not be concluded? Or is this sentence about the principle of not undertaking a sub-analysis with deliberate aim to reject the hypothesis or data dredging?></p> <p>Proposed change (if any): -</p>
20	251-252	<p>Comment: <To have a conflict of interest is different from acting on a conflict of interest, therefore add the word potentially. ></p> <p>Proposed change (if any): <A conflict of interest is a situation in which a person involved in a research project has a professional or personal interest sufficient to potentially influence the objective exercise of his/her judgment towards any activity of the project.></p>

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10. Annex 2. List of criteria included in the “Current status of quality management implementation” survey

Study

Study protocol development and protocol deviations, criteria:

Documented expert review

Recommended or standard template for protocol

Reporting and communication of study results, criteria:

Documented expert review

Recommended or standard template for study report

Qualification of external vendors/service providers/data providers/analysts (if applicable), criteria:

Documented process

Defined criteria for assessment

Note: the categorization of these criteria were later considered not appropriate – but only after the survey was completed

Ensure independent research in case of unconditional grant

Written documentation of scientific independence

Note: this criterion is taken up in the code of conduct and not further addressed here.

Security

Protection of data on premises, servers and individual work stations, criteria:

Use of security logs

Designated and controlled areas for data storage

Access only for authorized personnel

Log on with multi-character passwords

Storage after study end for minimum of five years


Data storage index present for audit and inspection purposes

Protection of identifiable and confidential data, criteria:

Replacing of overt personal identifiers by clear identifiers, keeping the mapping key separate from the pseudo-anonymized data

All researchers must sign a confidentiality agreement

Back-up criteria:

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At least one (but preferably multiple) back-up(s) in different location(s)

Data

Process of electronic data transfer, criteria:

Only sent data from one place to another by secure methods (encrypted)

Data processing (and statistical programming if applicable), criteria:

System-generated audit trails in place

Application/execution of standard consistency checks

Availability of Statistical Analysis Plan (SAP) prior to data analysis

Use of validated statistical software

Annotated study programming (programming giving explanatory notes for each step)

Standard process for statistical programming control (i.e. review or double-programming)

Archival of SAP and statistical programs

Human protection

Organisation and responsibilities for data privacy, criteria:

Formally documented that data is legally obtained

Presence of (an) allocated person(s) responsible for data privacy

Ethical review board: process for obtaining Ethics Committee approval of an appropriate level

Informed consent: obtain ethics approval of informed consent or waiver of informed consent

Expertise

Ensure sufficient qualification of study personnel, criteria:

Ensure a principal investigator is qualified and appointed

Have written organisational charts and personnel tasks in place


Training system, criteria:

Initial and continued training

Continuous documentation of training status and certification

Commitment, criteria:

Allocation of resources and qualified personnel prior to study start

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Managing quality

Existence of quality cycle, criteria:

Continuous cycle of planning, adherence, control and assurance, improvements of all processes in place

Written policies and procedures for main processes/activities and systems, criteria:

Quality plans

Quality manuals

Periodic review and update

Record management policy

Urgency processes/escalation policies

Document control and document management , criteria, criteria:

Review and approval process

Traceability of records (version control processes / timestamps)

Controlled document management system

Audit and inspection preparedness, criteria:

Inspection plan available

Periodic internal audit


Documentation of audit reports and results

Periodic check of study facilities and equipment

Deviation management; corrective and preventive actions and follow-up

Ensure adherence to procedures/compliance management, criteria:

Written compliance management process

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Annex 3: Results of Consortium Survey on implementation status of Quality Management



BACKGROUND

Opportunity identified to align quality management standards among stakeholders

- Review of guidelines for observational research on aspects and criteria of quality management
- Survey as **baseline inventory** of importance and current implementation of quality management across stakeholders

Quality management standards to be taken up in CoC and best practices. Criteria to be tested in the POC.



2



REVIEW OF THE GUIDELINES

Guidelines and legislation reviewed:


- GVP Module I
- GVP Module VIII
- GPP
- GEP
- International Ethical Guidelines for Epidemiological studies

Assessment of the elements of quality control and assurance described in the commonly referred good practice guidelines and regulatory guidance applicable to observational research.

To identify indicators of implementation of quality management for use in the survey to assess their current implementation status



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SURVEY

The final survey consisted of 48 quality criteria across 6 categories:

- Study – protocol, report and responsibility for execution
- Human protection – ethics, informed consent, privacy protection
- Expertise – qualification of the personnel, training
- Data – analysis plan, programming
- Security and storage – access, archiving facilities
- Quality Management – written procedures

Criteria captured specific process elements and standards of quality management

Survey questions were aimed to determine baseline status among stakeholders of:

- The adhered importance of quality aspects
- Implementation of quality management

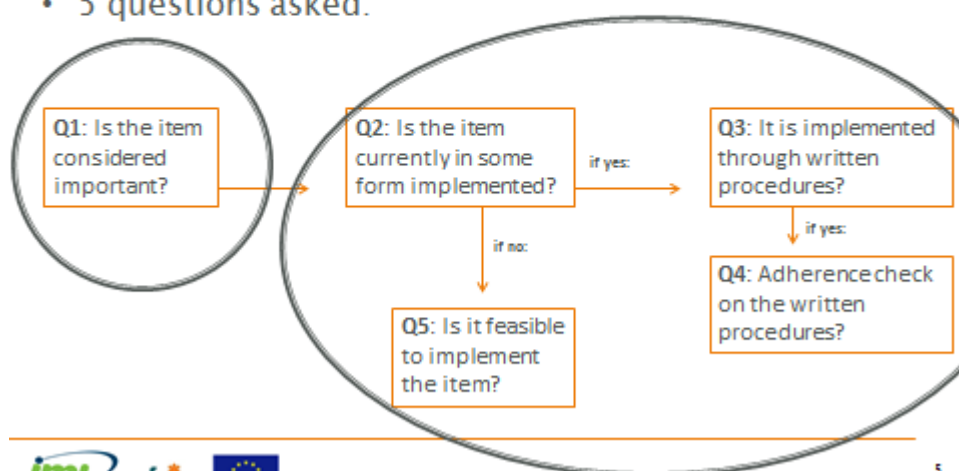


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METHODOLOGY (SURVEY SET-UP)

- 48 quality criteria across 6 categories,
- 5 questions asked:



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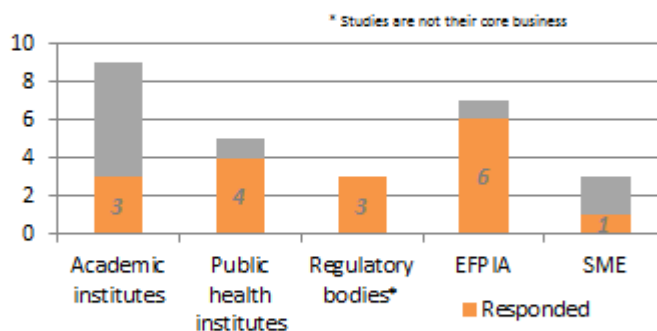


RESPONSE RATE

Total of 17 responses only from full partners (63%);

No responses from associate partners

3/17 respondents did structurally not answer the questions for the aspects



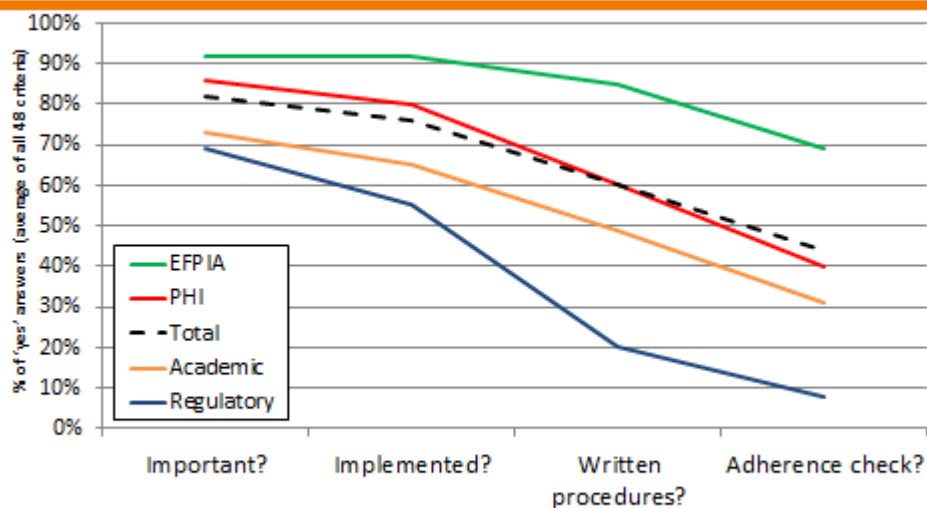
Of note for the interpretation: the overall outcome rate is influenced by unequal division of respondents across stakeholder groups




6



TREND MANAGEMENT OF QUALITY

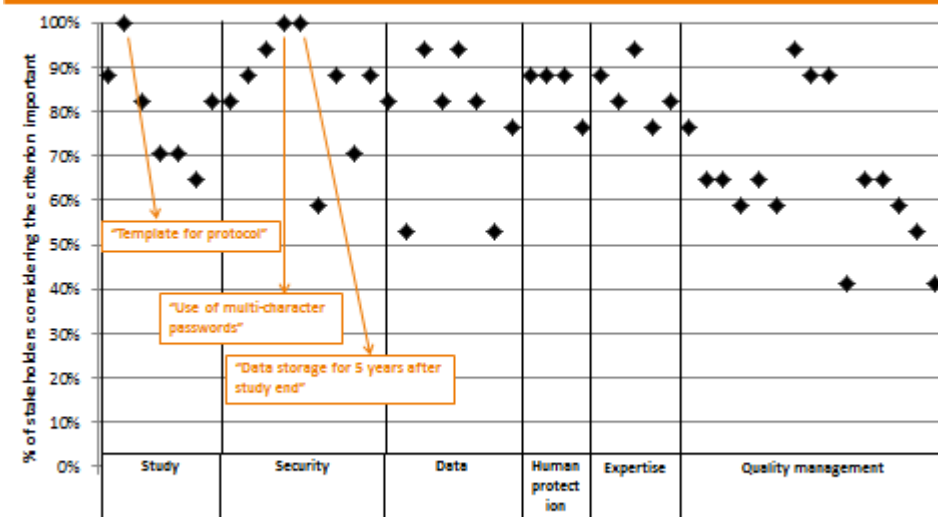


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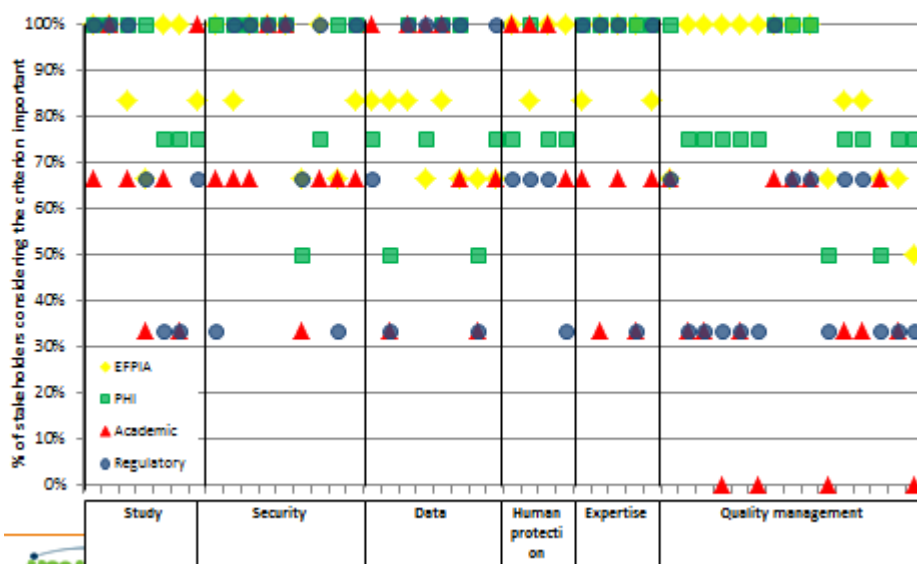
CONSENSUS ON IMPORTANCE OF QUALITY CRITERIA → N_{RESP.} = 17




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CONSENSUS ON IMPORTANCE OF QUALITY CRITERIA



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SUMMARY OF FINDINGS ON IMPORTANCE

- On average 77% of the partners considered a quality criterion important
- Only 3 criteria were considered important by all respondents
 - Data storage after study end for minimum of five years
 - Log on to servers and work stations with multi-character passwords
 - Use of a standard template for the study protocol
- More consensus on importance within organizational type
 - Academic → 11 criteria
 - PHI → 21 criteria
 - EFPIA → 22 criteria
 - Regulatory → 19 criteria
- This shows relatively low inter-organizational consensus on what is important



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SUMMARY OF FINDINGS ON WRITTEN PROCEDURES

- On average 52% of the partners used written procedures (i.e. SOP or WI) as implementation of a quality criterion
- This question gave a large number of unknowns/unclears. 143 in total (*out of 17 respondents x 48 aspects = 816 answers in total*)
- Out of all non-yes answers, 38% were unknowns/unclears
- Within PHI there is no agreement between the 4 respondents on any of the quality aspects
- Answers to the aspects belonging to the category 'processes for managing quality' show that EFPIA and PHI are likely to work with SOP's, WI, written quality procedures, whereas academic institutions and regulatory bodies* not so much. *Cave regulatory bodies indicated that studies were not their core activity



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SUMMARY OF FINDINGS ON ADHERENCE CHECKS

- On average 39% of the partners performed adherence checks on their written procedure
- This question gave an even larger number of unknowns/unclears; 227 in total
- Out of all non–yes answers, 46% were unknowns/unclears
- Within Academic institutes there are 31 quality aspects on which none of the respondents answered ‘yes’ to this question; within regulatory bodies that was the case for 37 aspects
- As comparison, within EFPIA there were 0 aspects that none of the respondents performed adherence check on



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SUMMARY OF FINDINGS ON FEASIBILITY TO IMPLEMENT

- When a criterion was not currently implemented, on average 15% of the partners was willing/able to implement it in some form
 - Though many respondents found this question difficult to answer (high no. ‘unknown’ and many comments)
- Items with high rate of non–implementation were found across all 6 categories, except for the theme “security and data integrity”.
- In the theme “data transfer” the variation in implementation rate was largest
- Overall highest non–implementation rate was found at the “quality management process” part



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ADVANCE DEFINING MINIMUM QUALITY CRITERIA


The suggested list of minimal quality criteria is made up of the quality criteria mentioned in the survey that **were considered important by at least xx% of respondents.**

Cut-off point (% of respondents that considered the aspect important)	Number of criteria that remain
70%	34 (out of 48)
75%	30 (out of 48)
80%	26 (out of 48)
85%	18 (out of 48)
90%	8 (out of 48)

ADVANCE DEFINING MINIMUM QUALITY CRITERIA

Criteria that are not selected if importance threshold < 80%

1. Documented process for qualification of external vendors (75%)
2. Defined criteria for assessment of external vendors (69%)
3. Data storage index present for audit and inspection purposes (75%)
4. All researchers must sign a confidentiality agreement (79%)
5. System-generated audit trails in place (79%)
6. Standard process for statistical programming control (i.e. review or double-programming) (67%)
7. Obtain ethics approval of informed consent or waiver of informed consent (76%)
8. Inspection plan available (64%)
9. Periodic check of study facilities and equipment (71%)
10. Deviation management; corrective and preventive actions and follow-up (75%)
11. Written compliance management process (58%)

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KEY FINDINGS AND LIMITATIONS

=====Key findings=====

1. Especially theme 'processes for managing quality' gave large variation in answers
2. Good consensus on the importance and more variation on the implementation
3. Highest scores on importance are regulatory required aspects and criteria (according to GVP module I and VIII)

=====Limitations=====

1. Multiple roles in one organization
2. Choice of words is very important to avoid misconceptions – elements of quality management should be better described and explained to allow for common interpretation and evaluation.

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11. Annex 4: List of Good pharmacovigilance practice (GVP) requirements and recommendations related to observational PAS and PASS applicable in the European Union (EU) - conducted voluntary and per obligation

This overview lists the obligations and recommendations for MAH and the investigators applicable in the European Union (EU). as indicated by shall (legal requirements) or should (recommendation) clauses in the GVP Modules VIII (EMA/813938/2011 Rev 2*, 4 August 2016) for PAS (post-authorisation study) and PASS (post-authorisation safety study) with MAH involvement, imposed or conducted voluntary. For the context and for the latest revisions, MAH and researchers should always consult the full GVP modules at


http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp.

O = Legal obligation ; V = recommendations in Good pharmacovigilance practices (GVP); - = no legal obligation or recommendation, * not applicable for secondary database studies


Description	GVP	PAS	PASS ⁶	
			Imposed as obligation	Conducted voluntary
General				
Non-interventional PASS shall be conducted in accordance with the following provisions: • DIR Art 107m	VIII		O	O
Non-interventional PASS shall be conducted in accordance with the following provisions: • DIR Art 107n-q, REG Art 28b and IR Art 36-38			O	-
EU and national requirements shall be followed for ensuring the well-being and rights of the participants [DIR Art 107m(2)].	VIII	O	O	O
The legislation on data protection must be followed in accordance with Directive 95/46/EC of the European Parliament and of the Council on the	VIII	O	O	O

⁶ In the light of DIR Art 1(15), a post-authorisation study should be classified as a post-authorisation safety study when the main aim for initiating the study includes any of the following objectives:


- to quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another medicinal product or class of medicinal products as appropriate, and investigate risk factors, including effect modifiers;
- to evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);
- to evaluate the risks of a medicinal product after long-term use;
- to provide evidence about the absence of risks;
- to assess patterns of drug utilisation that add knowledge regarding the safety of the medicinal product or the effectiveness of a risk management measure (e.g. collection of information on indication, off-label use, dosage, co-medication or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern);
- to measure the effectiveness of a risk management measures.

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Description	GVP	PAS	PASS ⁶	
			Imposed as obligation	Conducted voluntary
protection of individuals with regard to the processing of personal data and on the free movement of such data				
Marketing authorisation holders and investigators shall follow relevant national legislation and guidance of those Member States where the study is being conducted [DIR Art 107m(2)].	VIII	O	O	O
The marketing authorisation holder has the responsibility to ensure that the study is not a clinical trial	VIII	O	O	O
The study is not to promote medicinal product [DIR Art 107m(3)].	VIII	-	O	O
Protocol				
Written study protocol.	VIII		O	O
Standard formats and content of protocol as per GVP guidelines and IR Annex III. Feasibility or pilot studies that are part of the research process should be described in the protocol. (for details of the format and the content see GVP module VIII and the Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies available on the EMA website).	VIII		O	V
ENCePP methodological standards	VIII		V	V
ENCePP Checklist for study protocol	VIII		V	V
The study protocol should be developed by individuals with appropriate scientific background and experience.	VIII		V	V
Relevant scientific guidance should be considered by marketing authorisation holders and investigators for the development of study protocols, the conduct of studies and the writing of study reports,	VIII		V	V
Procedures for the collection, management (including a review by the marketing authorisation holder if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol.	VIII		O	V
The timing of the submission of progress reports should be agreed with the relevant competent authorities and specified in the study protocol when they have been agreed before the study commences.	VIII		V	V
The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the	VIII		O	V

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Description	GVP	PAS	PASS ⁶	
			Imposed as obligation	Conducted voluntary
study start should be documented in the protocol in a traceable and auditable way including the dates of the changes.				
The qualified person responsible for pharmacovigilance (QPPV) or his/her delegate should be involved in the review and sign-off of study protocols	VIII		V	V
Protocol submission				
The draft study protocol shall be submitted by the marketing authorisation holder to the PRAC or to the national competent authority of the Member State that requested the study if the study is conducted in only one Member State [DIR Art 107n(1)] When a letter of endorsement has been issued by the PRAC, the marketing authorisation holder shall forward the protocol to the national competent authority of the Member State(s) in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol [DIR Art 107n(3)].	VIII		O	-
The marketing authorisation holder shall submit the study protocol in English except for studies to be conducted in only one Member State that requests the study according to DIR Art 22a. For the latter studies, the marketing authorisation holder shall provide an English translation of the title and abstract of the study protocol [IR Art 36].	VIII		O	-
The marketing authorisation holder shall submit any substantial amendments to the protocol, before their implementation, to the national competent authority or to the PRAC, as appropriate [DIR Art 107o]	VIII		O	-
The marketing authorisation holder's pharmacovigilance contact person at national level should be informed of any study sponsored or conducted by the marketing authorisation holder in that Member State and have access to the protocol.	VIII		V	V
Protocol registration				
Registration in EU PAS register	VIII		O	V
The study protocol (and its updates) should be uploaded in the Registry as soon as possible after its finalisation (preferably <2 weeks after finalisation) and prior to the start of data collection. Redactions should be justified and kept to the minimum necessary for the objective aimed by the redaction process. The protocol should be identified as "Redacted protocol" and the non-redacted protocol	VIII		V	V

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Description	GVP	PAS	PASS ⁶	
			Imposed as obligation	Conducted voluntary
should be entered in the register as soon as possible and preferably within two weeks after the end of data collection.				
The date of study registration in the electronic study register shall be included as a milestone in the final study report [IR Annex III].	VIII		O	-
Listing of PASS in appendix 4 of the PSUR according to GVP Module V.	VII		O	V
Information on non-interventional PASS in the pharmacovigilance plan of the Risk Management Plan as PASS as described in GVP Module V.	V		V (category 1-2)	V (category 3)
The marketing authorisation shall be varied to include a PASS obligation as a condition of the marketing authorisation and the risk management plan, where applicable, shall be updated accordingly [REG Art 10a(3), DIR Art 22a(3)]	VIII		O	V
Contracts and qualifications				
The investigators are qualified by education, training and experience to perform their tasks.	VIII		V	V
The research contract between the marketing authorisation holder and investigators should ensure that the study meets its regulatory obligations while permitting their scientific expertise to be exercised throughout the research process. In the research contract, the marketing authorisation holder should consider the provisions of the ENCePP Code of Conduct.	VIII		V	V
Payment to HCP(s) is restricted to compensation of time and expenses incurred [DIR Art 107m(4)]	VIII		O	O
The marketing authorisation holder and the investigator should agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.	VIII		V	V
Study conduct				
The marketing authorisation holder shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the medicinal product concerned [DIR Art. 107m(7)].	VIII		O	O

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Description	GVP	PAS	PASS ⁶	
			Imposed as obligation	Conducted voluntary
Any information which may influence the B/R balance to be reported to NCAs of MS where the product is authorised and to the Agency	VIII		O	O
Recording of any suspected adverse reaction in the Union or in third countries brought to attention of the MAH with primary data collection in accordance with GVP module VI	VI	O*	O*	O*
Reporting of suspected adverse reactions in studies with primary data collection to competent authorities in accordance with GVP module VI	VI	O*	O*	*O
The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.	I		O	O
The marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection [IR 12, IR Art 36].	VIII		O	V
The marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected [IR Art 12, IR Art 36].	VIII		O	V (This is however an obligation for pharmacovigilance data arising from the study)
Record management and data retention shall follow the provisions of IR Art 12.	VIII		O	O
Reporting				
The marketing authorisation holder shall submit the abstract of the final study report and the final study report in English except for studies to be conducted in only one Member State that requests the study according to DIR Art 22a. For the latter studies, the marketing authorisation holder shall provide an English translation of the abstract of the final study report [IR Art 36].	VIII		O	-
Upon request from a national competent authority, progress reports shall be submitted to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)]. The content of any progress report, if applicable, should follow a logical sequence and should include all the available data that are judged relevant for the progress of the study.	VIII		O	O

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Description	GVP	PAS	PASS ⁶	
			Imposed as obligation	Conducted voluntary
The final study report shall follow the format described in the Guidance for the Format and Content of the Final Study Report of Non-Interventional Post-Authorisation Safety Studies [IR Annex III)	VIII		O	V
Reports of adverse events/reactions summarised as part of any interim safety analysis and in the final study report	VIII	O*	O	O
The marketing authorisation holder shall submit a final study report, including a public abstract, to the national competent authority or to the PRAC as soon as possible and not later than 12 months after the end of data collection, unless a written waiver has been granted by the national competent authority or the PRAC, as appropriate [DIR Art 107p(1)].	VIII		O	-
Communication of final manuscript of any article to be published to the Agency and Member States where the product is authorised within two weeks after first acceptance of publication	VIII		V	V
Inclusion in PSURs of study results relevant to the benefit-risk of the medicinal product with a consideration of their potential impact on the marketing authorisation	VII	O	O	O
Inclusion of PASS final study report completed during reporting period in the regional (EU) appendix of the PSUR	VII		O	V
The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.	VIII		O	O
If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.	VIII		V	V
The marketing authorisation holder shall evaluate whether the study results have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities or the Agency an application to vary the marketing authorisation [DIR Art 107p(2)]. In case a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics (SmPC) and package leaflet within the determined timetable for implementation [DIR Art 107q(2)].	VIII		O	V
The marketing authorisation holder initiating, managing or financing a non-interventional PASS should communicate to the Agency and the	VIII		V	V

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Description	GVP	PAS	PASS ⁶	
			Imposed as obligation	Conducted voluntary
competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication				