Vaccine 35 (2017) 1844–1855

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

The ADVANCE Code of Conduct for collaborative vaccine studies

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ARTICLE INFO

Article history:
Received 12 September 2016
Received in revised form 5 February 2017
Accepted 20 February 2017
Available online 9 March 2017

Keywords:
Code of conduct
Study team
Transparency
Scientific integrity
Public health

ABSTRACT

Lessons learnt from the 2009 (H1N1) flu pandemic highlighted factors limiting the capacity to collect European data on vaccine exposure, safety and effectiveness, including lack of rapid access to available data sources or expertise, difficulties to establish efficient interactions between multiple parties, lack of confidence between private and public sectors, concerns about possible or actual conflicts of interest (or perceptions thereof) and inadequate funding mechanisms. The Innovative Medicines Initiative's Accelerated Development of VAccine benefit-risk Collaboration in Europe (ADVANCE) consortium was established to create an efficient and sustainable infrastructure for rapid and integrated monitoring of post-approval benefit-risk of vaccines, including a code of conduct and governance principles for collaborative studies. The development of the code of conduct was guided by three core and common values (best science, strengthening public health, transparency) and a review of existing guidance and relevant published articles. The ADVANCE Code of Conduct includes 45 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). Each topic 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 ADVANCE Code of Conduct with a core set of roles and responsibilities. It is hoped that adoption of the ADVANCE Code of Conduct by all partners involved in a study will facilitate and speed-up its initiation, design, conduct and reporting. Adoption of the ADVANCE Code of Conduct 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.

Contents

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[1] The ADVANCE Code of Conduct was developed by a working group of Work Package 1 of the ADVANCE Consortium, which also included Peter Arlett (European Medicines Agency, United Kingdom), Jorgen Bauwens (University of Basel, Switzerland), Phillip Bryan (Medicines and Healthcare products Regulatory Agency, United Kingdom), Anna Cantarutti (PEDIANET, Italy), Catherine Cohet (GSK Vaccines, Belgium), Stephen Evans (London School of Hygiene and Tropical Medicine, United Kingdom), Patricia Felicetti (Italian Medicines Agency, Italy), Cédric Mahé (SP MSD, France), Kari Natunen (University of Tampere, Finland), Mirna Robert (Novartis, Netherlands), Raphaele Roten (Crucell Holland, Netherlands), Nynke Rots (National Institute for Public Health and the Environment, The Netherlands), Miriam Sturkenboom (Erasmus University Medical Centre, Netherlands) and Jane Whelan (GSK, Netherlands).

http://dx.doi.org/10.1016/j.vaccine.2017.02.039
0264-410X/

1. Introduction

Monitoring the benefits and risks of vaccines is a complex and critical activity that involves multiple participants. Decisions to be made at the planning stage are numerous: 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 rapid action needs to be taken and a (updated) benefit/risk assessment is needed within short timelines. The 2009 (H1N1) flu pandemic threw light on the limited capacity to meet this challenge at the European level and to rapidly collect and analyse post-marketing data on vaccine exposure, safety and effectiveness. Following the authorisation of the first H1N1 influenza vaccines in Europe in September and October 2009, the core risk management plan adapted to the H1N1 strain included the definition of adverse events of special interests (AESIs), recommendations for observed-to-expected analysis for signal detection and requests to vaccine manufacturers for post-authorisation safety studies [1,2]. However, the lack of a system to collect vaccination statistics at European level and background incidence rates for several AESIs led regulators to compile exposure data through ad-hoc surveys and to rely on assumptions for the expected rates of adverse drug reactions, which provided a wide range of possible values for the Standardized Morbidity Ratio (SMR) for the same set of data [2]. European data for background incidence rates for AESIs became available in December 2009 and January 2010, after the peak of the vaccination campaign [3–5]. Preliminary data from an industry-sponsored safety study were also available in January 2010, the first results of epidemiological studies conducted in Europe were made public at the end of August 2010, once the pandemic was over [6,7] and estimates of vaccine effectiveness were published relatively late after the vaccination campaign. Those from the large I-MOVE European network were published in January 2011 [8], although preliminary reports were available earlier to some regulatory and public health authorities. The main issue limiting the capacity for a timely collection, analysis and reporting of data was identified as the lack of a formal established European infrastructure providing rapid access to available data sources on large populations and supporting collaborations and common approaches for data collection [1,2,9]. In addition, lessons learnt from the pandemic underlined the difficulties to establish efficient interactions between multiple stakeholders (regulators, public health agencies, vaccine manufacturers), insufficient coordination of communication activities among interested parties, regulatory requirements unknown to other concerned bodies than vaccine manufacturers, disparate access to relevant data sources, concerns about possible or actual conflicts of interest and lack of mechanisms for the funding of studies [1,9]. On the basis of these findings, the Innovative Medicines Initiative framework [10] was used in 2013 to set up the Accelerated Development of Vaccine benefit-risk Collaboration in Europe, (ADVANCE) [11], a public-private consortium to work towards the vision of "An efficient and sustainable infrastructure for rapid and integrated monitoring of post-approval benefit/risk of vaccines under clear governance rules meeting the common interest of all main stakeholders". Such a framework would allow regulators, public health authorities and vaccine manufacturers to make fast, informed decisions regarding vaccination strategies. To support effective collaborations and clear governance for the conduct of studies, a best practice guidance would include a code of conduct and recommendations for governance models, quality management and communication. Guidelines on the planning and conduct of pharmacoepidemiological studies already exist at national and international levels and were reviewed to identify whether they fulfil the needs of ADVANCE for a structured guidance applicable to every step of the conduct of collaborative vaccine studies. This field has a number of key characteristics such as 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. Such guidance should also serve the needs of public health surveillance, which requires the same level of scientific standards and transparency as in research. This article presents the ADVANCE Code of Conduct developed in this context.

2. Method

2.1. The ADVANCE project

ADVANCE revolves around three pillars needed for the intended framework: data sources (WP3), methods (WP4) and best practice mechanisms (WP1) (Fig. 1). These pillars are strengthened by leverage of existing results, initiatives and projects, through synergetic collaboration (WP2), refined and validated through selected proof of concept studies (WP5) and leading to blueprint or model for benefit-risk monitoring of vaccines in Europe (WP7). WP6 provides the necessary coordination, management and communication backbone of the project. The ADVANCE Code of Conduct is part of best practice mechanisms to be developed by WP1.

2.2. Guiding principles

The ADVANCE Code of Conduct was developed on the basis of a core set of guiding principles [12]. 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,

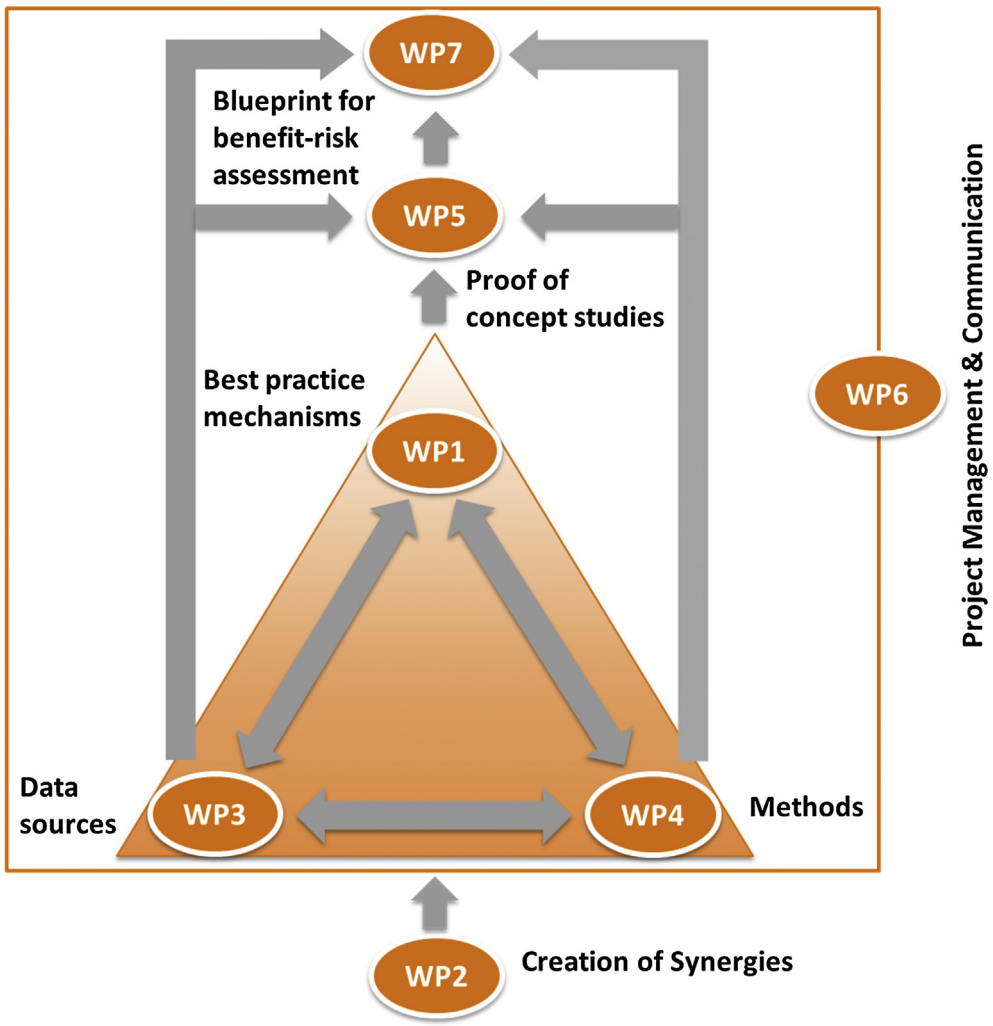

Fig. 1. Core structure of the IMI ADVANCE project (WP: Work Package).

initiation, design, conduct and reporting of post-marketing vaccine benefit-risk monitoring activities. The survey was conducted during a consortium general assembly with 47 attendees from different stakeholders (15 public health institutes, 10 academia, 6 regulatory agencies, 11 vaccine manufacturers, and 5 other groups). The survey helped identify guiding principles and topics to be addressed in the code of conduct.

2.3. Review of existing guidelines

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 [13], literature search and screening of the reference lists of retrieved documents in order to identify whether any current guideline would fit the needs for recommendations.

2.4. Development of the ADVANCE Code of Conduct

Each guideline was reviewed by two members of ADVANCE WP1 who extracted relevant recommendations for the predefined topics. For each topic, all recommendations were reviewed and either removed or kept and reworded as necessary. New recommendations were developed as needed. The resulting draft code of conduct was published on the ADVANCE website for a public consultation outside ADVANCE from 29 September to 15 November 2015. The call for comments was disseminated as widely as possible among relevant learned societies and individual experts. The text was revised based on the comments received.

In the course of the development of the code of conduct, the concept of the *study team* emerged as a core element of every study to endorse key roles and responsibilities. It was therefore developed simultaneously to the code of conduct.

3. Results

3.1. Guiding principles

Among the 14 candidate values initially identified (science, ethics, improving public health, excellence, integrity, transparency, open dialogue, independence, partnership, trust, reliability, respect, accountability, commitment), those ranking first overall in the survey of consortium partners 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 their 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"). These three principles were also ranked first by representatives from public health institutes and academia, and any two of them were ranked first by representatives from other groups. *Independence* and *ethics* appeared only in the top three values selected by representatives of the regulators and vaccine manufacturers group, respectively (further information on this survey is available in a separate document [14]). The principles of best science, strengthening public health and transparency were used to guide the identification of topics to be addressed in the ADVANCE Code of Conduct and the development of the recommendations.

3.2. Review of guidelines

A total of 44 guidelines and documents were identified from the literature review and suggestions provided during the public consultation. From these, 31 were considered relevant to provide useful information on at least one topic of the ADVANCE Code of Conduct. They are listed in the reference section of Appendix A. Among widely used guidelines in pharmacoepidemiology, the Code of Conduct [15] of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) provides standards for scientific independence and transparency of research that require registration of the study (with the study protocol and abstract of study results) in the EU Post-Authorisation Studies (PAS) Register [16] and making other study documentation available upon reasoned justification. As one of the provisions is 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). It was therefore not considered comprehensive enough to meet the objectives of ADVANCE but its core principles of scientific independence and transparency were integrated into the ADVANCE Code of Conduct. Other important guidance includes the Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE) [17] and the Good Epidemiology Practice (GEP) of the International Epidemiological Association (IEA) [18]. The GPP proposes practices and procedures that should be considered to help ensure the quality and integrity of pharmacoepidemiological research, including detailed guidance for protocol development, roles and responsibilities, study conduct, communication, reporting of adverse events and archiving. The GEP addresses four general ethical principles for research (Autonomy, Beneficence, Non-maleficence and Justice) and proposes rules for good research behavior in relation to working with personal data, data documentation, publication, exercise of judgment and scientific misconduct. The GPP and the GEP do not address all topics to be covered by the ADVANCE Code of Conduct but they were used as an important source of guidance.

3.3. The ADVANCE Code of Conduct

During the public consultation, a total of 386 comments on the draft code of conduct were received from 20 organisations and individuals, including from ISPE, the ENCePP network, patients' and health care professionals' associations and vaccine manufacturers. The comments are available upon request to the corresponding author.

The resulting ADVANCE Code of Conduct includes 45 recommendations in 10 topics: Scientific integrity, Scientific independence, Transparency, Conflicts of interest, Study protocol, Study report, Publication, Subject privacy, Sharing of study data and Research contract (Appendix A). For each topic, it 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 distinguishes two levels of recommendations: 28 are considered critical and should be applied in all studies ("must") and 17 should be considered for all studies but may be less critical for the study governance ("should"). In case of public health crisis requiring faster conduct of a study, investigators may focus on recommendations with a "must". The recommendations are listed for each topic by their "must" and "should" status in Table 1 and described in Appendix A.

The concept of the study team is presented in Appendix B. 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 from within or outside the study team to assess the background and reasoning for the decisions taken.

4. Discussion

Guiding principles may provide a solid foundation for the multiple decisions that need to be taken at all stages of the planning, design, conduct and reporting of vaccine studies [12]. The three core and common 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 Code of Conduct was developed and agreed by a wide range of different organisations: regulatory and public health authorities (including the European Medicines Agency and the European Centre for Disease Prevention and Control), vaccine manufacturers and academic organisations. It should be adopted in all studies and it should be adopted entirely and by all individuals and organisations involved in the study, provided that compliance with the applicable regulatory requirements and legislation can be maintained.

It is believed that its adoption by all partners involved in a study will facilitate and speed-up the initiation, design, conduct and reporting of studies by avoiding lengthy discussions on principles of collaborations and on contractual agreements. It is recommended that adoption of the ADVANCE Code of Conduct 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.

With 45 recommendations, the ADVANCE Code of Conduct is a comprehensive document that can be seen to be complex, and this perception may be 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 those on drugs. The implementation of the ADVANCE Code of Conduct will be monitored through a review of vaccine post-authorisation safety and effectiveness studies submitted to regulatory and public health authorities, review of protocols of non-interventional studies registered in the EU PAS Register and search for statements on its use in studies published in scientific journals. Its implementation in each study can also be part of a structured monitoring by external bodies such as scientific committee or ethical committee. The experience will show whether the ADVANCE Code of Conduct contributes to the facilitation of vaccine studies by improving interactions between partners, supporting access to observational

Table 1
Summary of the recommendations of the ADVANCE Code of conduct for collaborative vaccine studies.[a]

Topic	Recommendations to be applied in all studies ("must")	Other recommendations to be considered for all studies ("should")
1. Scientific integrity	1. All study team members are qualified to fulfil their role	
	2. All study team members act in accordance with core values of honesty, accuracy and objectivity	
	3. Study team members adhere to IEA Good epidemiological practice and ISPE Good pharmacoepidemiological practices	
2. Scientific independence	4. Study is conducted without undue influence of any financial, commercial, institutional or personal interest in a particular outcome of the study	5. Autonomy of members of study team for making scientific decisions in their organisation is documented
	6. Scientific independence is safeguarded by clear and transparent roles and responsibilities, peer review process, transparency measures and disclosure of all funding sources	
3. Transparency	7. Study is registered in a publicly accessible database before the start of data collection or extraction	11. Final study report or summary is uploaded in publicly accessible database where study is registered
	8. Sources of funding are made public at the time of registration, in the protocol and in the presentation of results	12. After study completion, study information is made available from outside the study team in a collaborative approach
	9. Declarations of Interests (DoI) are made available at an early stage of the study, regularly updated and disclosed	13. In case of primary data collection, participants in the study or their representatives may receive main study results and interpretation thereof
	10. All comments received on study protocol and results with impact on the study are documented	
4. Conflict of interest	14. Actual or potential conflicts of interest (and perceptions thereof) are addressed at the planning phase of the study. Research contract includes a description of the management of conflicts of interest. All DoI are made publicly available	15. A standard form is used to declare all interest that may lead to conflicts
5. Study protocol	16. A study protocol is drafted as one of the first step in any research projects	18. The process for reaching an agreement on the design options of the study is agreed beforehand
	17. Study protocol is developed by persons with relevant expertise	22. Detailed draft protocol undergoes independent scientific review
	19. Protocol includes a section with ethical considerations involved and information on funding, affiliations, potential conflicts of interest, data protection and incentives to subjects. Protocol is approved by relevant research ethics committee	23. Protocol is registered in publicly accessible database before the start of data collection
	20. Protocol includes description of each party to study design, protocol writing and work programme	
	21. Regulatory obligations and recommendations applicable to the study are described	
	24. Changes to the protocol that may affect the interpretation of the study are identifiable and reported in the study report	
	25. Key statistical analyses are described	
6. Study report	26. Set of principles are followed for reporting results including documentation of important safety concerns and deviations from protocol or statistical analysis plan, sources affecting data quality, strengths and limitations, and sources of funding	27. STROBE statement and internationally agreed guidelines are consulted when analysing and reporting data
		28. Draft study report undergoes independent scientific review
		29. Study report or summary of the results is included in the publicly accessible database
7. Publication	30. All study results are made publicly available. Authorship of publications follows the rules of ICMJE	32. Preliminary or partial results of discontinued study are reported and identified as such
	31. Research contract allows the principal investigators and relevant study team members to publish study results independently from the funding or data source. The study requester/funder may provide comments	
	33. Procedures are in place to rapidly inform regulatory and public health authorities of study results, independently from submission of a manuscript	
8. Subject privacy	34. Privacy of study subjects in relation to personal data is core principle of any medical research	
	35. In case where personal data are collected, the applicable legislation is followed	
9. Sharing of study data	38. Sharing of study data is based on a written request specifying the ground of the request. The study team verifies the compliance of the request with the data protection legislation	36. There is an open and collaborative approach to sharing study data with persons from outside the study team
	39. Requests for data sharing are justified based on public health interest	37. Data are shared only after the study report is finalised
	41. Analyses performed with shared data follow the provisions of the ADVANCE Code of Conduct	40. Study team or delegated committee takes the decision to share study data
10. Research contract	42. The research contract does not lead investigators, directly or indirectly, to act against the principles of the Helsinki Declaration or applicable legal or regulatory obligations	44. Unique multiparty contract is preferred in cases where several parties interact
	43. Clarity and transparency are key elements of the research contract	45. The research contracts indicates that the study will follow the ADVANCE Code of Conduct and provides core information

[a] A description of each recommendation is provided in Appendix A with definitions and references. IEA: International Epidemiological Association; ISPE: International Society for Pharmacoepidemiology; ICMJE: International Committee of Medical Journal Editors; STROBE: STrengthening the Reporting of OBservational studies in Epidemiology.

data sources and increasing confidence in their results. It would be speculative to state that the code of conduct could have prevented the difficulties met during the A/H1N1 pandemic [1,9], but we believe that its adoption may have facilitated contractual agreements between different stakeholders, use of larger amount of private funding for studies, earlier sharing of results with regulatory and public health authorities and possibly faster decision-making. The ADVANCE Code of Conduct will be subject to periodic revisions and the authors welcome comments and proposals for improvement. Revised versions will be published on the ADVANCE website (www.advance-vaccines.eu).

Prior presentation

A draft version of the Code of Conduct was presented as a poster at the 31st Conference on Pharmacoepidemiology and Therapeutic Risk Management, 2015 (Kurz X. et al. The ADVANCE Code of Conduct: a tool for vaccine benefit-risk monitoring in Europe. Pharmacoepidemiology and Drug Safety 2015;24(S1):189).

Funding

The ADVANCE project has received support from the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement no. 115557, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in kind contribution.

Declarations of interest

XK, PM and LvdA have no interest to declare. VB and SG are employees of GSK Vaccines. VB owns restricted shares in the GSK group of companies as part of his employee remuneration. FS was an employee of Sanofi Pasteur MSD at the start of ADVANCE and moved to IRD (a public institution) during the course of the project. He declares no conflict of interest in relation to this article.

Disclaimer

The views expressed in this article are those of the authors only and not of their respective institution or company.

Appendix A. The ADVANCE Code of Conduct

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 members of the study team must be qualified to fulfil their role in the study.
2. All members of the study team 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 members must adhere to the IEA Good epidemiological practice [2] and the ISPE Good pharmacoepidemiological practices [3] without exception. They 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: [4–10]

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 the study team members 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.
   - 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: [3,11–14]

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

7. 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].
8. 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.
9. Declarations of Interests of the study team members 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.
10. 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.
11. The final study report should be uploaded into the publicly accessible database where the study is registered.
12. 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.
13. 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]

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

14. 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.
15. The study team members 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]

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

16. 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.
17. The study protocol must be developed by study team members 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).
18. The process for reaching an agreement on design options 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.
19. 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.
20. 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.
21. A specific section must describe the regulatory obligations and recommendations applicable to the study.
22. A detailed draft protocol should undergo independent scientific review by experts that did not participate to its writing and are not anticipated to be directly involved in the study as investigators. Their recommendations are not binding but should be made available.
23. The study protocol should be registered in a publicly accessible register before the start of data collection or extraction.
24. 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.

25. 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]

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

26. 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 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.
27. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement and other internationally agreed guidelines should be consulted when analysing and reporting data.
28. 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.
29. 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: [3,12,16,22–24]

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

30. 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.
31. The research contract must allow the principal investigator and 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.
32. 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.
33. 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: [3,16,25–27]

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

34. Privacy of study subjects in relation to personal data is a core principle of any medical research and divulgation 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.
35. In case where personal data are collected or used in a study, the applicable legislation, in Europe Directive 95/46/EC, must be followed.

Additional reading: [2,14,27,29]

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

36. 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.
37. Data should be shared only after the study report has been finalised.
38. 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.
39. 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.
40. 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.
41. 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: [12,30]

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:

- Funding is provided by a party or parties to other party or parties for a research project;
- Part of the research project is sub-contracted by a 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

42. The 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.
43. Key elements of the research contract are clarity and transparency: all relevant aspects must be covered in a way that is understandable by all the parties concerned.
44. 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.
45. The research contract 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: [2,3,12,16,31]

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Appendix B. The study team

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.

Study team composition

The main criterion for membership is a documented scientific expertise relevant for the research question. As such, membership should not be based solely on affiliation with a specific partner in the project or with any specific type of organisation. Study team members should have sufficient autonomy within their respective organisation, and their organisation 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.

Roles

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

Responsibilities

Responsibilities of the study team include:

- Ensuring compliance with the ADVANCE Code of Conduct and other relevant guidelines. 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.
- 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.
- Organising peer-review with external experts or an external advisory board for important study documents such as the study protocol and study report.
- Delivering the protocol and the study report according to the recommendations set out in the ADVANCE Code of Conduct.
- Ensuring posting of the study protocol and results.
- Publishing the study results, 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.
- Reviewing requests for study data sharing and organising data sharing as applicable.

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.

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