Ann Ist Super Sanità 2020 | Vol. 56, No. 3: 257-259
DOI: 10.4415/ANN_20_03_01

EDITORIAL

The increasing need for a new Italian legislation to facilitate execution of observational studies assuring ethics and the highest standards of scientific and methodological quality

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To make solid and effective decisions, healthcare professionals, patients, regulatory agencies and policy makers need the best available evidence on a given research question, that comes from systematic reviews of the literature, from randomized controlled clinical trials (RCT, experimental studies) and also from observational research, that greatly contributes to generate evidence in the real world setting (real world evidence, RWE). Unfortunately, in the last decade scientists conducting observational studies in Italy faced several obstacles, mostly caused by ambiguous terminology and definitions, and by a national legislation that need to be updated. This has been causing not only long and expensive authorization processes (which make Italy less competitive, if compared with other European countries), but has been producing also potential limitations for an effective control of the study protocols quality and for the design of innovative research projects. In particular, the Italian legislation currently regulates only observational studies on medicinal products [1], leaving the conduction of other observational studies without a normative reference.

Recently, the Italian Society of Pharmaceutical Medicine (SIMeF) together with the Istituto Superiore di Sanità (ISS), the University of Milano Bicocca (Centro di Ricerca Interuniversitario Healthcare Research & Pharmacoepidemiology), the Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI) and the Società Italiana di Farmacologia (SIF) activated a working group to formulate specific recommendations for the definition of the new forthcoming national legislation on observational studies, in the framework of law 11 January 2018, n. 33 [2] and legislative Decree 14 May 2019, n. 52 [3]. The recommendations were later formally approved by several other Italian scientific societies* and the underlying concepts were positively discussed with representatives of the Italian Drug Agency (AIFA), the Health Ministry and the Data Privacy Authority.

* List at February 2020: Centro di Ricerca Interuniversitario Healthcare Research & Pharmacoepidemiology Università degli Studi di Milano Bicocca; Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI); Istituto Superiore di Sanità (ISS); Società Italiana di Farmacologia (SIF); Società Italiana di Medicina Farmaceutica (SIMeF); Associazione Farmaceutici Industria (AFI); Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP); Società Italiana di Statistica Medica ed Epidemiologia Clinica (SISMEC); Società Italiana per Studi di Economia ed Etica sul Farmaco e sugli Interventi Terapeutici (SIFEIT); Gruppo Italiano Data Manager (GIDM).

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The scope of the recommendations was limited to observational studies defined as "collection and analysis for scientific purposes of epidemiological, administrative, clinical and biometric data related to single human subjects". According to these recommendations, the new provision should be mandatory and should regulate all the types of study conducted with observational methodology, within biomedical and health field, promoted by public or private organizations. Therefore, the new regulation should cover observational studies with or without drugs, with or without additional diagnostic procedures, with primary or secondary data uses, and should also include studies based on databases and complex data sources (for example data collected directly from patients via digital tools).

In this context, each study protocol should receive a single competent evaluation, with a multi-sites and nation-wide validity: this modus operandi is coherent with that indicated by the European Regulation n. 536/2014 [4] for clinical trials. Local evaluations at sites level should be limited to verify the presence of all the needed resources (human, material and organizational) for correctly executing the study and to evaluate the promoter's proposal for administrative agreement. This promoter's should also be facilitated using standard templates (*e.g.* privacy information model, administrative contract) with a nation-wide validity and by a standardized national fee for the evaluation of observational studies across the country.

Authors suggest also some practical steps to make this new authorization process feasible. It could be useful to define a list of Ethics Committees certificated by the Ministry of Health as "expert" Ethics Committees for the evaluation of observational studies. Sponsor/Promoter could therefore obtain a single evaluation submitting the documentation to one of these certificated Ethics Committees which should have appropriate expertise to evaluate typical complexities related to observational studies, such as the documentation related to the privacy as well as the methods for collecting and storing biological samples or for access to database of biological samples.

Special attention should be addressed to observational studies where, for methodological reasons, the study protocol requires additional diagnostic and evaluation procedures, e.g. being these procedures known and used in normal clinical practice but not routinely applied for the cases to be included in the study. In these specific situations, authors recommend that the study protocol contains a specific section dedicated to illustrating the scientific rationale and the methodological reasons for this choice. Further, the subject must provide a specific written consent, based on a comprehensive information about the purposes, the nature and the methods of carrying out additional examination/s, and potential inconveniences associated with the procedures. It is also fundamental that the costs of additional procedures should not be borne by the National Health Service (NHS) nor by the subjects, but fully covered by the sponsor/promoter. Moreover, the Ethics Comittee should evaluate the need for the sponsor/promoter to stipulate a specific insurance if the additional procedure is evaluated as invasive and risky for the subject.

Recommendations also consider some additional actions: fundamental information on all type of observational studies should be entered in a national registry; a mapping of new and already existing healthcare databases and registries should be activated to allow investigators to have access to high quality data, also thanks to nationwide, transparent rules; participation to observational studies shouldn't be limited to physicians only but also permitted to other healthcare professionals, once they are adequately trained on ethical, methodological, regulatory and technical aspects. Last but not least, forthcoming Italian regulation should be aligned with already existing EU regulations and guidelines – especially EU Good Pharmacovigilance Practice (GVP) and the General Data Protection Regulation (GDPR) – also by means of preliminary consultations among the stakeholders to harmonize different approaches and definitions and to solve some existing issues.

According to the authors' opinion, the above summarized recommendations can facilitate the execution of observational studies in Italy assuring both ethics and the highest standards of scientific and methodological quality. For this reason, the authors strongly encourage to adopt these guidelines to define the new national legislation on observational studies.

Acknowledgements

Thanks to SIMeF colleagues Silvia Ferrara (Janssen) and Antonietta Caputo (Roche) for the contribution in the definition and writing of the recommendations. Special thanks to Michela Masoero (Medineos) for the precious contribution in coordinating the inter-societies working group.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings.

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