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Observational studies - The Cinderella of the Italian research system

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Abstract

Observational trials are crucial to assess the generalizability in the real world of evidence deriving from registration studies. Despite the unquestionable importance of this type of studies, Italian researchers have had to face many obstacles over the years, mainly due to ambiguous definitions and to a complex but at the same time incomplete legislation. The regulatory adjustments to the European Regulation 536/2014 have further complicated the operating and operational framework, making observational research a real "Cinderella" of the Italian system.

Keywords

Observational trials, regulation, prospective studies, retrospective studies, Italian research system

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Introduction

Although experimental studies are the gold standard for demonstrating the comparative effectiveness of a health technology (drug, medical device, surgical procedure), observational studies can also provide important, complementary and supplementary information to those obtained with experimental methods.

Observational trials can be used to assess the generalizability in the real world of evidence deriving from registration studies, as in larger/different populations (e.g. more fragile, complex or rare) or in those less selected and more heterogeneous, observed for longer periods of time, to investigate the use (including clinical appropriateness), the safety, effectiveness of the drug as a whole (effectiveness) and the effectiveness also taking into account the cost (cost-effectiveness) of a healthcare technology or of the diagnostic-therapeutic pathways experienced by patients.

Despite the unquestionable importance of this type of study, Italian researchers have faced many obstacles over the years, mainly due to ambiguous definitions and a complex yet at the same time incomplete legislation.

This condition has caused a growing need for a new legislation to facilitate the execution of observational studies, assuring ethics and the highest standards of scientific and methodological quality until the publication of a programmatic document containing formal proposals to the institutions.[1,2]

Orphan studies

The first difficulty related to observational research in Italy is the absence of a formal competent authority. If the Italian Medicine Agency (AIFA) supervises pharmacological observational studies, all others are in "no man's land", and this has led numerous problems over the years. It has also resulted in the lack of an actual legislation: until a year ago, the only official texts were the guidelines that AIFA formulated in 2008 regarding pharmacological observational studies.[3] This recommendation contained information on the correct definition of a pharmacological

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observational study, as well as practical indications on the procedures necessary to obtain the authorization to start the research.

This process required, in the case of a prospective study, a notification to the competent authority and a request for an opinion from the ethics committees (EC) of all the involved centers, one of which had to be identified as the coordinator. In the case of a retrospective study, a notification to the committees (with the application of a silent-consent period of 60 days) would be sufficient, unless the regulation of the involved EC expressly required the release of a formal opinion.

For a long time this process, characterized by a profound procedures reiteration, has been the source of delays for activating observational studies, above all those with a high number of involved centers or promoted by entities lacking infrastructure dedicated to regulatory activities, as in the context of non-profit research.

In the absence of precise rules, these guidelines have always been "transferred" onto observational studies of other types, except for the need for initial notification to AIFA.

What is 'observational'?

Another critical issue is related to the correct definition of observational research. The only definition reported in the Italian legislation concerns pharmacological observations, defined as studies involving a drug that meets the following conditions: 1) the drug must be prescribed according to the indications for use; 2) the prescription must be part of normal clinical practice; 3) the decision to prescribe the drug to the individual patient must be entirely independent from that of including the patient in the study; 4) diagnostic and evaluation procedures should correspond to current clinical practice.

Over time, however, the scientific community has begun to raise many concerns regarding possible ancillary practices and which and how many of them could cause the study to lose the label 'observational'.

In the absence of official responses, and above all due to the lack of a competent authority that could take charge of such requests for clarification, the evaluation was entrusted to the individual ethics committees, often with profoundly heterogeneous results.

An example is given by biological studies, which for some committees may be considered observational, for others drug-free and device-free interventional studies.

The wind of (promised) change

The advent of the new European legislation on clinical trials,[4] and the regulatory steps that would be necessary in Italy to comply, has led the scientific community to hope for more appropriate rules also for observational research.

A hope shattered by the publication of the new decree that regulates observational and non-profit studies,[5] which has once again given regulatory relevance only to observational pharmacological research, leaving the other types of observational studies again in a worrying grey area.

Despite this serious gap, the decree introduced an important step forward: the possibility, only for prospective pharmacological observational studies, to benefit from a single opinion at national level, as for the interventional trials.

The decree also announced the formulation of new AIFA guidelines (scheduled for early April 2022 but not yet published) and the implementation of an electronic register which will serve as a database and operational tool. This register will be effectively active starting from 31 January 2023.[6]

The competent ethics committees

Italy's adaptation to Regulation 536/2014 also required a profound overhaul, still in progress, of the ethics committee structure. In 2018 the National Coordination Center of Ethics Committees was established, a body based at AIFA which was to have coordination and control functions with respect to the other ECs in Italy. For a long time, this was the only step towards the definitive reorganization, until the identification of three national ethics committees.[7] Two of these committees have headquarters in AIFA and will deal with pediatric studies and trials involving the use of advanced therapies respectively; the third, based at the Italian Institute of Health, will evaluate studies promoted by public research bodies.

An important subsequent step was the publication of four implementing decrees,[8,9] two of which established the roles and responsibilities of the future forty territorial ethics committees. These committees, which will be identified by their regions, will have to deal with evaluating studies (interventional with drugs or devices and pharmacological observational) that do not fall within the areas of competence of the national ones.

Furthermore, each region will have to decide whether to entrust the evaluation of all other types of research (for example: non-pharmacological observational, interventional without drugs or devices) to the forty territorial ethics committees or whether to set up accessory committees, which will be defined as 'local'.

This varied landscape opens up several operational possibilities regarding the methods of requesting an ethical opinion for observational studies, with many points still to be clarified (Figure 1). First of all: will there really be an obligation to pass through multiple committees for retrospective studies?

The black hole of privacy

It may seem strange, but observational research was the most compromised by the privacy restrictions following the forced entry into the General Data Protection Regulation 2016/679 (GDPR).[10]

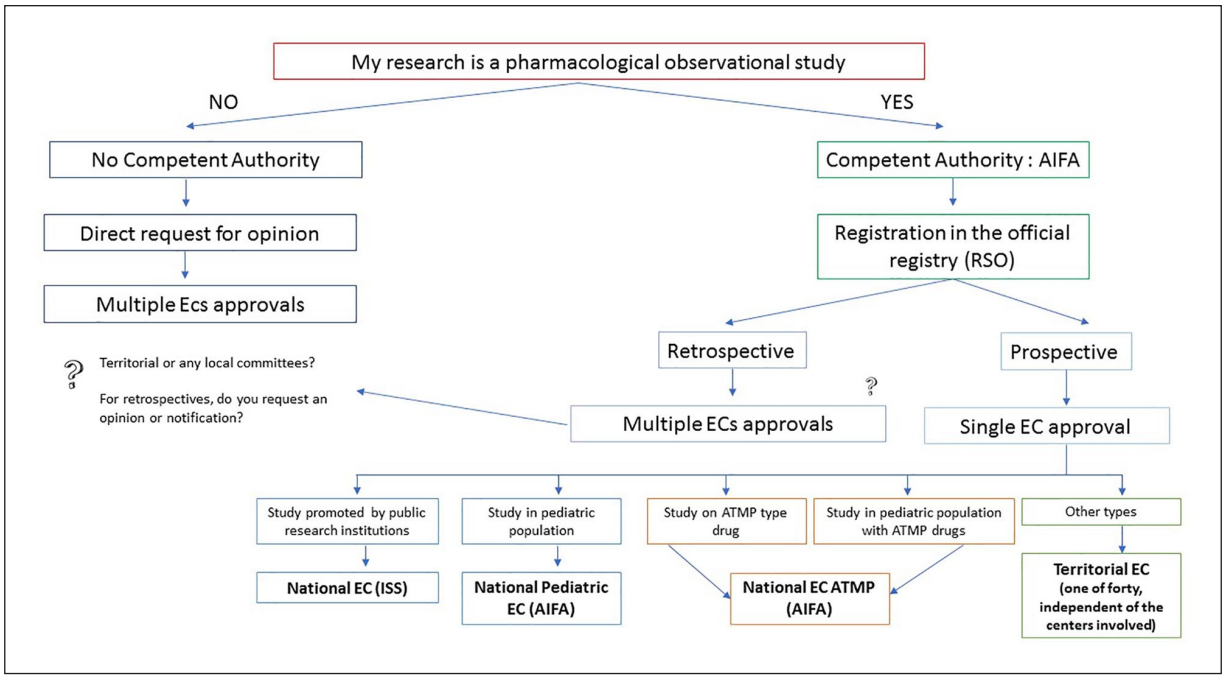

Figure 1. Decision-making algorithm for the regulatory process of observational studies depending on study type.

Although the European scientific community immediately denounced the possible deleterious effects of the GDPR on clinical research,[11-14] in Italy the situation has become even more complicated in 2018 due to the new national legislation on privacy.[15] With this decree, Italy does not recognize the protection of public health as a legal basis for the processing of personal data, which therefore only becomes permitted if it is possible to collect the consent of the involved party or if the research is conducted in accordance with the law. If is impossible to obtain the consent of the involved person (e.g. deceased patients, ethical or organizational reasons), then the procedure for starting the study becomes even more complex, and requires prior authorization from the privacy guarantor.

A condition that mainly affects and hinders retrospective observational research, raising legitimate questions on how much the protection of individual ethics should prevail over that of collective ethics and on the importance of preserving the scientific process.[16]

Future perspectives

Observational studies, considered for years as the 'Cinderella' of Italian research, deserve different attention, both in terms of regulatory affairs and practical management.

The first desirable change would be a law that covers all 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).

For all these studies, a single evaluation at the national level should be enough, possibly issued by ethics committees that are broadly competent in the field of observational research, as suggested by Petrini et al.,[1] and possibly with a more linear decision algorithm than illustrated in Figure 1. A vision recently officially revived by the National Coordination Center of Ethics Committees, which published a note in which it invites, albeit without regulatory pretensions, to apply common sense in the management of all observational studies, without distinction of typology.[17] At the moment this possibility is only contemplated for prospective pharmacological observational studies, and it is at least a questionable decision.[5]

This strategy has already proved successful in many other European countries. In France, for non-interventional studies there is one Ethic and Scientific committee (called *CESREES*) that centralized the process, with only a single approval. Likewise, in the United Kingdom there is a centralized ethics process for studies that involve secondary data collection via the national health system, so only a single approval is required. Spain has even produced a single decree dedicated to all non-interventional studies again with a single centralized approval.[18]

It would also be desirable that the promoters were required to use the documentation in accordance with standardized templates, which are currently mandatory only for experimental trials. Furthermore, it is probable that the task of the competent EC would be facilitated if

there were an official definition of studies that require additional diagnostic and evaluation procedures.

Certainly, the training of the evaluation bodies will be able to make the difference as it will happen more and more often that observational studies concern real-world data collection which could end up in a regulatory package for a market access request, as assumed by the European Medicines Agency.[19]

In this regard, it would be useful to be able to count on a competent authority, with decision-making power both in the pharmacological and non-pharmacological fields.

The most urgent aspect is certainly to create a channel of dialogue with the privacy guarantor and with those who make the decisions, in order to simplify the secondary use of the data and to allow the conduction of some observational studies even in the absence of consent.

Simplification does not necessarily mean lower qualitative and ethical standards, and Italy has an urgent need to move away from the image of an uncompetitive nation in the field of research.[20,21]

Observational research can be a great point to start from and other Member States have already shown a feasible way.

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