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OPINION PAPER

# OBSERVATIONAL RESEARCH: WHY IS IT SO NEGLECTED?

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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 undeniable importance of the topic, in Italy numerous difficulties persist, mainly linked to two aspects: the impact of privacy regulations, especially in the case of retrospective research; a gap between methodological and regulatory definition. Here we aim to provide an overview of the state of the art of observational research in Italy to draw attention to this issue and spark debate within the international scientific community. In the absence of a competent authority that can enact laws in this context, it is important that the scientific community is made aware of the issues and puts up a united front to foster a cultural change.

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**Impact statement:** The purpose of this paper is to stimulate a discussion within the scientific community aimed at accelerating the publication of new guidelines on observational drug studies and, hopefully, the publication of standards covering all types of observational research.

**Key words**: *observational research; observational studies; privacy; regulatory; orphan studies.*

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Clinical research based on both experimental and observational methods has the fundamental goal of producing the best available evidence on a given research question to allow solid and effective decisions. Traditional experimental studies, long regarded at the "gold standard" of evidence, can provide solid results related the efficacy of a health technology, while pragmatic randomized controlled trials can produce information related comparative effectiveness. However, also observational studies, with care in the interpretation of the results, can provide important, complementary and supplementary information useful for the decision making at both regulatory and clinical levels (1).

In particular, observational studies can be used to assess the generalizability in the real world of those evidences deriving from premarketing studies, collecting data in larger, less selected and more heterogeneous/different populations (*e.g.*, more fragile, complex or rare patients), observed for longer periods of time to investigate clinical appropriateness, safety, effectiveness and cost-effectiveness of an healthcare technology or of the diagnostic-therapeutic pathways experienced by patients.

For these reasons, in the span of just two decades and a half, the landscape of medical regulatory science has undergone a remarkable transformation. The notion of leveraging evidence from observational studies for regulatory purposes, once considered implausible, has now gained more legitimate and valuable approach. Regulatory agencies such

as the Food and Drug Administration (FDA) and the European Medicine Agencies (EMA) are not only endorsing but also championing the integration of Real-World Data (RWD) into the evaluation matrix for new medical treatments and health technologies.
Unfortunately, despite the unquestionable importance of the clinical research based on observational methods, Italian scientists today still face severe obstacles in promoting and conducting this type of studies, mainly caused by an inadequate local legislation, also characterized by ambiguous terminology. The scientific community has long been calling for solutions to this problem (2, 3).

## THE GAP BETWEEN THE METHODOLOGICAL AND NORMATIVE DEFINITIONS OF OBSERVATIONAL STUDY

From a purely methodological point of view, it is quite simple to discern between an experimental study, in which participants are "actively" assigned to one or more interventions according to a study protocol, to evaluate the effects of those interventions on subsequent health-related outcomes, and an observational one in which patients receive the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol, so that investigator simply collect "passively" data regarding the effect to the observed expositions (4).

On the other hand, at European level regulatory definition is more confusing due to a misleading terminology where the term "non-interventional" is traditionally used to indicate both a passive exposition to the determinant object of the study but also the use of additional diagnostic and evaluation procedures, which however normally do not modify the observational nature of the study (5).
To complicate the situation, in Italy we have the lack of a single national agency able to deal with all type of observational studies. In fact, Ministry of Health is responsible solely for what concerns medical devices, Italian Drug Agency (AIFA) for what concerns drugs, but neither AIFA nor the Ministry deal with all other fields of observational research. This lack of rules often leads to confusion and differences in interpretation (**Figure 1**).
In addition, it is necessary to consider that as "orphan" studies do not have a competent authority, it is not possible to have laws or guidelines (**Table 1**).
As a result of this situation, in Italy the only type of observational research fully regulated is the one on drug (6). According to the EMA definition, AIFA defines a study as "non interventional" if the following criteria are cumulatively met:

1. The drug is prescribed in the indications for use authorized in Italy;
2. The prescription of the drug is part of the normal clinical practice;
3. The decision to prescribe the drug to the individual patient is completely independent from

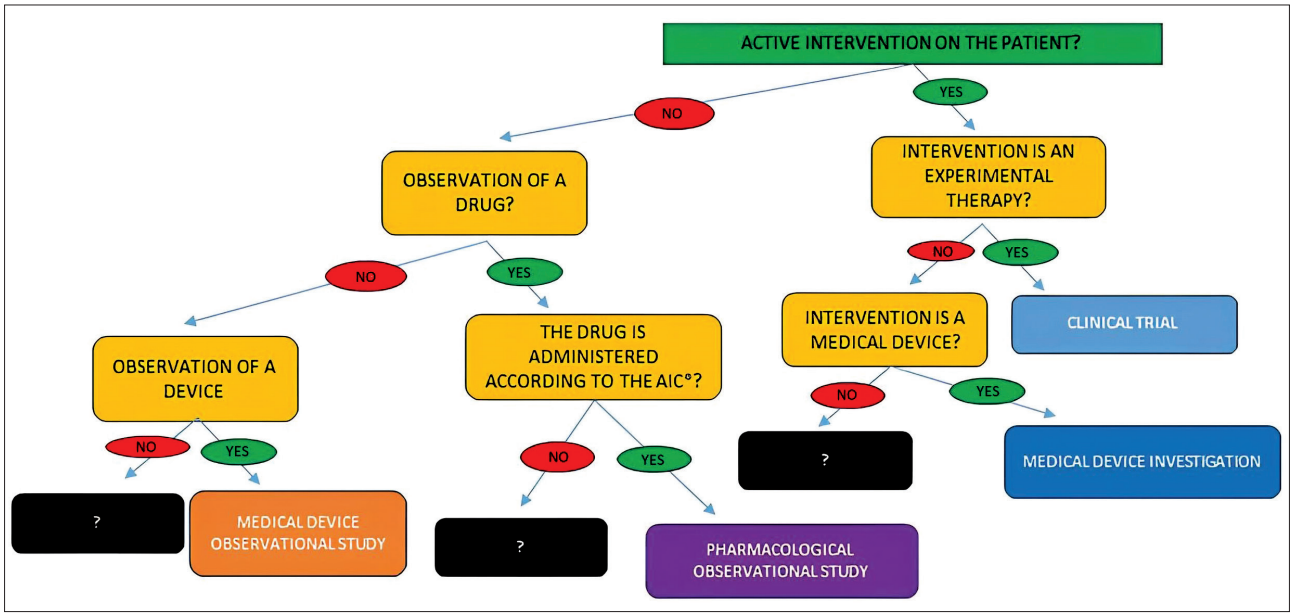


**Figure 1.** *Regulatory label decision-making algorithm. °AIC, Autorizzazione all'immissione in Commercio (Marketing Authorization).*

**Table 1.** *Main reference law by type of study.*

| STUDY TYPE | LAW |
|---|---|
| **Clinical trials** | REGULATION (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745 |
| **Studies on medical devices** | REGULATION (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC Red Eu DM https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745 |
| **Studies on *in vitro* medical devices** | REGULATION (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746 |
| **Pharmacological observational studies** | Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci https://www.aifa.gov.it/documents/20142/516919/111.88758.1186138046156a0be.pdf |
| **Interventional studies without drug or device** | None |
| **Observational studies (not on drug or device)** | None |

the decision to include the patient in the observational study;

4. Diagnostic and evaluative procedures correspond to current clinical practice.

This definition over time has proven inadequate, generating two major perplexities:

- Why can I observe only drugs administered according to clinical practice? Off-label use is widespread in some settings, and observational research could gather very important data for scientific progress (7).
- Do additional diagnostic procedures really turn an observational study into an experimental one? Which are the criteria that precisely defines what is and what's not "clinical practice"?

## THE AGE-OLD ISSUE OF THE ADDITIONAL DIAGNOSTIC AND EVALUATIVE PROCEDURES

From a methodological perspective, it is clear that the addition of diagnostic and evaluative procedures aimed at answering the study questions does not transform an observational study (passive exposition to the determinant) in and an experimental one (active exposition); *e.g.*, questionnaires do not alter the observational nature of the study as well as that the presence of pharmacokinetics and pharmacogenomics analyses, regardless of the frequency of sampling and the amount of blood drawn.

However, there's no doubt that additional procedures pose at least two sets of problems:

- they can impact the ethics of the study, if they are invasive or even minimally dangerous or painful;
- must be treated in compliance with the observational nature of the study.

According to a recent statement of the "National coordination center for ethics committees" (1), it is recommended that additional clinical procedures (*i.e.*, not foreseen for the specific subject in current clinical practice) may be considered admissible if necessary for the purposes of the study as long as they do not alter the current diagnostic and therapeutic strategy and as long as they are expressly declared and evaluated by the Ethics Committee considering among others factors: a) how acceptable they are in an observational study in terms of invasiveness/dangerousness, also taking into account the relevance of the study in scientific/health terms, and its methodological quality; b) the absence of conditioning, on the basis of this information, of the subsequent management of the patient, and whether the failure to use any information acquired in the management of the patient is acceptable; c) the adequacy of the information provided to the participating subject on the additional procedures envisaged by the study. Moreover, the general practitioner should receive an information note, and the costs of additional procedures should

not burden either the National Health Service or the individual. The assessment of the extent and acceptability of any risks linked to the additional procedure is the responsibility of the Ethics Committee which, where necessary, may request an insurance policy paid by the study promoter.

## THE IMPORTANCE OF THE REGULATORY LABEL

Being able to define a correct regulatory label for research is crucial for at least two main aspects.
The first motivation is related to study insurance. The current research legislation, which suffers from the strong bias of being "pharmacocentric", provides a binary interpretation: interventional study requires a specific study insurance; observational study not. The law currently does not provide specifics for all cases that fall into the "gray area". Does a biological study require insurance? Does a study with additional procedure require insurance? Unfortunately, there is not a single answer, and often each evaluating body gives a personal opinion to the question, posing major problems where a study involves the evaluation of multiple ethics committees.

Moreover, depending on the study's regulatory label the regulatory process could be very different. The observational drug study involves an initial registration step on the Registro degli Studi Osservazionali (RSO) portal set up by AIFA; thereafter, the fate currently depends on the directionality of the study. If prospective, according to a recent ministerial decree (8), the study can benefit from a single ethical opinion with national validity; if retrospective, on the other hand, it must follow the old process, characterized by multiple steps: expression of opinion by a coordinating ethics committee (or just acknowledgement, depending on what is provided for in the regulations of that committee) and acceptance/rejection of the single opinion by the satellite committees, with the ability to request changes only to patient documents (*e.g.*, informed consent). What if the study has dual directionality? Good question: each committee has its own opinion on this.
Steps from multiple ethics committees is also required in case of non-drug observational studies and non-drug and non-device interventional studies, with an added complexity: the committees in charge of evaluation might not be national and/or territorial ones but additional committees (local), at the discretion of each region.
If this complexity were not enough, some regions decided to modify the national process through local acts.

## IMPACT OF PRIVACY

Observational research has certainly been the hardest hit by privacy legislation, at least in Italy. The national law (9) that allowed the implementation of the General Data Protection Regulation (GDPR) (10), in fact, introduced numerous obstacles and restrictions.
First of all, it was no longer possible, except with a fairly complex procedure of prior authorization by the guarantor authority, to conduct retrospective studies in the absence of explicit informed consent. This resulted in a strong disinterest in retrospective studies or, in many cases, in the activation of projects with strong methodological bias (*e.g.*, inclusion of only those patients for whom consent could be collected).

Other complications concern studies involving the collection of biological specimens since technically at this moment it is not possible to donate the specimen for research purposes as well as to ask the patient for an initial "expanded" consent to future research. The Italian guarantor authority requires a progressive approach: collection of an initial consent for the collection of the specimen for future research purposes followed by a subsequent new passage from the patient at the time of the actual conduct of future investigations. An approach that is ill-suited to the timing and very essence of research, so much so that the scientific community has repeatedly spoken out against it (11-13).
In fairness, it must be said that for both issues there is no single line of thought. The law in question give way for different interpretations, and this constitutes an additional layer of complexity

## FUTURE PERSPECTIVES

Recent changes in national privacy legislation (14) would seem to have solved the problem of retro-

spective studies by eliminating the need for prior consultation although, as has already happened, there seem to be very conflicting interpretations.
Further simplifications are expected to be introduced with the new guidelines on observational drug studies. First, the single nationwide opinion will also be extended to projects of a retrospective nature; the drug observational study label will also be applied even if the observation should concern not a drug administered according to the Marketing Authorization (AIC, Autorizzazione all'Immissione in Commercio) but in an off-label mode; the only constraint: the study must be retrospective.
Important steps forward but unfortunately not enough; the biggest issue remains to be solved: no one's child studies. The lack of a research agency above the parties, which can legislate even outside the drug and medical device, makes it impossible to translate the few simplifications introduced to all studies, shackling observational research, despite the relevance of the topic, to a minority and decidedly inadequate role.
While waiting for a political answer, what could the scientific community do? Certainly, the training of professionals plays a major role and should be promoted at all levels (ethics committees, clinical research infrastructure). Furthermore, a greater comparison between all the nation's ethics committees would be extremely useful, so as to achieve an appropriate level of homogeneity, both procedural and decisional, in those contexts where legislation does not provide answers. Last, but not least, open a channel of dialogue with the two bodies that could change the fate of observational research: the Ministry of Health and the Data Protection Authority.

## COMPLIANCE WITH ETHICAL STANDARDS

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