INTERVENTI

Aetiological observational studies and ethical clearance: An Italian co-created study in Tuscany Region (Central Italy)

Studi eziologici osservazionali e approvazione etica: uno studio italiano co-creato in Toscana

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ABSTRACT

In recent years, there has been an increase in ethical concern regarding the privacy of identifiable personal data and human biospecimens. Moreover, recent developments in active citizen participation in scientific research has highlighted ethical issues. This has reinforced the need for an adequate ethical and normative framework for observational studies. This paper focuses on the Italian situation and aims to highlight the need for specific national guidelines in non-clinical observational studies. To this end, a practical example is provided concerning the ethical approval process adopted in the co-created environmental epidemiological study entitled "Aria di Ricerca in Valle del Serchio" (Tuscany Region, Central Italy).

Keywords: aetiological epidemiology, ethics, citizen science, research involving human subjects

RIASSUNTO

Negli ultimi anni, è aumentata l'attenzione per le questioni etiche relative alla privacy dei dati personali identificabili e dei campioni biologici di origine umana. Inoltre, i recenti sviluppi nella partecipazione attiva dei cittadini alla ricerca scientifica hanno dato importanza a questioni etiche. Questo ha rafforzato la necessità di un adeguamento nel quadro etico e normativo per gli studi osservazionali. Questo contributo si focalizza sulla situazione italiana e intende mettere in luce la necessità di linee guida nazionali specifiche per gli studi osservazionali non clinici. A tal fine, viene riportato un esempio pratico relativo al processo di approvazione etica adottato nello studio epidemiologico ambientale co-creato dal titolo "Aria di Ricerca in Valle del Serchio" (Toscana).

Parole chiave: epidemiologia eziologica, etica, citizen science, ricerca che coinvolge soggetti umani

INTRODUCTION

Biomedical and epidemiological research involving human beings must be carried out following the universally recognized ethical principles outlined in the Declaration of Helsinki according to four general principles: autonomy, beneficence, non-maleficence, justice.[1] Over time, several guidelines have been provided to help investigators, sponsors and Ethics Committees guarantee that research studies observe this ethical framework when considering differences between experimental and observational studies.[2] However, while in experimental research, an international standardization of regulations has been adopted to apply these principles uniformly,[3] in observational research, a range of methods has been adopted, which varies from one country to another. In addition, ethical guidelines differ in length, scope, form, and purpose, due to the fact they are written by different organizations and serve different goals.[4] Due to this variation and normative lack, several problems have arisen. For example, there are difficulties in obtaining ethical review and clearance in multinational observational studies, as well as the publishing of study results in scientific journals in some cases where the authors and editors come from countries with different regulations in force.[5-8]

In recent years, increasing attention has been paid towards the potential harm for research subjects including non-physical harm caused by the disclosure of health-related information. As a result, there have been increased efforts to protect privacy. In addition, new aspects have been included in scientific research such as active citizen participation in research studies. These developments have reinforced the need for an adequate and shared ethical and normative framework concerning the variety of observational studies.[9]

Based on this framework, the paper focuses on the Italian situation and aims to highlight the importance of outlining specific national guidelines in non-clinical observational studies to be applied uniformly on Italian territory. To this end, a report is included in the present text concerning the ethical approval process of the co-created environmental epidemiological study entitled "Aria di Ricerca in Valle del Serchio".[10] This study, which was carried out in the Tuscany Region (Central Italy), falls under the field of aetiological observational studies[11] involving human subjects, including their personal data and biological samples. The expression "co-created" indicates a new way of performing scientific research in which researchers and citizens work together in all phases of the study.[12] Moreover, this investigation is particularly relevant because it was designed and carried out outside the context of health care institutions or research centres. Indeed, those who proposed the study are citizens together with a no-profit social enterprise.

ITALIAN FRAMEWORK: NO LAWS AND GUIDELINES FOR NON-CLINICAL OBSERVATIONAL STUDIES

In general, Italy aligns with the above-outlined international framework, but there are one or two gaps in its

legislation. Indeed, Italian legislation currently regulates only observational studies on medical products, leaving the non-clinical observational studies without a specific normative reference.[13]

Despite this legislative vacuum, ethical approval for observational studies which do not concern medical products is often required. This is due to a number of European and Italian dispositions regarding the collecting, storing, processing, and use of identifiable[14] personal data and human biological samples for scientific research in the medical, biomedical, and epidemiological fields.[15-20] These dispositions state researchers must ask for informed consent from the subjects from whom the data and samples originate and submit the study protocol to an Independent Ethics Committee for ethical clearance. This informed consent and the ethical clearance must be sought for both primary and secondary identifiable data/biospecimen uses. Nonetheless, in some specific cases, waivers of informed consent might be authorized by an Ethics Committee.

However, the Italian regulatory gap mentioned above and the lack of national guidelines for non-clinical observational research are generating non-uniform ethical approval paths.[21] As a result, due to this lack of clarity, research groups depend on the discretion of the Committee to which the study protocol is submitted.

The "Aria di Ricerca in Valle del Serchio" study fits into this non-uniform scenario. Firstly, the research group contacted the Commission for Research Ethics of the University of Florence to submit its epidemiological study protocol. This request was based on the fact that Research Ethics Committees established at universities evaluate and approve scientific studies outside clinical research. However, although some Research Ethics Committees in other Italian Regions usually review and approve observational studies that involve human biological samples, the Commission responded that the study did not fall under their authority, because a collection of human biological samples was part of the investigation. With this statement, the collection of human biological samples for research purposes was labeled as clinical research. The epidemiological study protocol was then submitted to the Regional Ethics Committee for Clinical Trials of the Tuscany Region. Consequently, the application process involved the use of documentation tailored to mirror clinical trial protocols and the ethical evaluation was requested to a committee established to review and approve clinical research, which consists of mainly clinical trials.

NEED FOR NATIONAL GUIDELINES IN NON-CLINICAL OBSERVATIONAL STUDIES

The main difference between clinical trials and non-clinical observational studies regards the fact that in clinical trials the researcher intentionally allocates exposure among the subjects enrolled in a study. This means that the investigator is responsible for what will happen to the subjects involved in terms of their physical and physiological risks and benefits due to the intervention received that is under study. Since the Helsinki Declaration in 1964, the ethical requirement to submit experimental study protocols to an Independent Ethics Committee for evaluation and clearance has been closely related to this responsibility.[22] In the light of possible damages inflicted on subjects, as a consequence of decisions taken by the investigator, an independent assessment regarding compliance with the ethical requirements of the studies to be conducted is therefore of paramount importance.

In non-clinical observational studies, there is no allocation of exposures, but rather the establishment of groups to be compared by identifying and selecting subjects whose exposed and unexposed status is determined by factors other than the study design, such as behaviour of the subjects involved, their place of residence, etc. In these cases, the investigator is not responsible for what will happen to the subjects enrolled through the exposures. At the same time, he/she maintains the responsibility concerning possible damage inflicted on subjects due to poor study design lacking scientific rigor – e.g., not attempting to reduce possible sources of error such as selection bias, information bias, and confounding effects – and due to non-compliance with ethical requirements that apply when data and/or biospecimens are directly collected from individuals and/or identifiable data/biospecimens are managed and used.[23,24]

Therefore, starting from the assumption that in both types of research study, investigators must abide by ethical principles of research involving human participants – such as sound scientific design, the minimization of risk, reasonableness of risks, informed consent, protection of confidentiality and privacy, returning individualized research results, obligations to communities,[25] avoiding and disclosing conflicts of interest –, it seems reasonable to suggest that specific national guidelines for non-clinical observational research should be drawn up and applied uniformly on Italian territory. These guidelines should provide clear instructions regarding the documentation in which the characteristics of non-clinical studies are considered. For instance, often the subjects recruited are healthy people instead of patients. Furthermore, the word 'controls' has a different meaning in a case-control study than in a clinical trial. Another aspect to be considered regards the stipulation of an adequate assurance based on the entity of the possible risk when this is the case. Moreover, in the light of new forms of investigation such as the case study reported below, the active role of citizens in scientific research should be also taken into consideration. Finally, epidemiologists should be in-

cluded among the members of Ethics Committees which evaluate non-clinical research studies.

THE LUCCA PILOT STUDY: CO-CREATION IN ENVIRONMENTAL EPIDEMIOLOGY

The Italian pilot study in the epidemiological research on environment and health entitled "Aria di Ricerca in Valle del Serchio" was part of the CitieS-Health project on Citizen Science and Environmental Epidemiology funded under the European H2020 programme for the three years, 2019-2021. The project was later extended until June 2022 due to the COVID-19 pandemic.[26]

The CitieS-Health project aimed to put citizens' concerns at the heart of the research agenda. Five pilot research studies on different aspects of urban environmental exposures and their relationship with health were conducted in five European countries. The pilots were set up as co-created studies following a participatory governance model carried out by both researchers and citizens, involving the latter in all steps of the study.[27]

The full engagement of citizens means two different roles. A new role as citizen scientists (active participants), e.g., debating and co-designing the study protocol together with researchers, as well as gathering data and analysing results. A traditional role as research subjects (passive participants), e.g., providing personal and health-related data.

The active role of citizens is a novel characteristic in research involving human subjects, which implies a normative and ethical shift. Indeed, in the traditional framework, legal rules and ethical requirements focus on protecting the rights and welfare of individuals involved in studies as passive participants and do not address issues concerning the involvement of individuals as active participants. In this case, ethics involves taking into consideration domains such as study design, data quality, data sharing, authorship, etc.[28] Hence, the question arises regarding how we can harmonise the active role of citizens with the current procedures of ethical clearance designed for traditional research involving human subjects.[29] In this regard, some obstacles and solutions addressed in the Italian pilot study are provided in the next Section.

CHALLENGES AND SOLUTIONS OF THE ETHICAL CLEARANCE PROCESS

The Italian pilot study in the Serchio Valley[30] was set up following concerns expressed by the local population regarding the possible effects of environmental pollution on health. The Valley is characterized by areas of natural and historical-cultural beauty on the one hand, and by important potentially polluting industrial installations, including a copper foundry with a potential risk of heavy-metal pollution, on the other. The area selected for the study consists of eight municipalities of the Valley. The investigation was coordinated by the no-profit Small and Medium Enterprise Epidemiologia&Prevenzione, in collaboration with the eight municipalities, the local environmental group 'La Libellula', and researchers of some Italian universities.

The epidemiological study protocol, which included biomonitoring, was written in collaboration with the most active citizens over the course of several meetings. The protocol specified a cross-sectional epidemiological survey regarding the prevalence of chronic kidney diseases in a representative sample of the resident population. Chronic kidney diseases were operationally defined based on the measurement of serum creatinine concentration and heavy metals taken from a blood sample and some base parameters taken from a urine sample. To this end, participants were asked to provide blood and urine samples. In addition, the laboratory results were related to information collected through a questionnaire on health status, lifestyle, individual characteristics, and occupational history.

It was also agreed to store a quota of the biospecimens for possible future research uses, complying with the rules concerning biobanking human samples. Therefore, the protocol described the procedures required to set up an outpatient clinic for the collection of blood and urine samples and a clinical lab to process and store them at a temperature of -80°C in a dedicated freezer. The protocol also foresaw asking for specific consent while respecting the privacy of individuals from whom the biological materials originated. Note that, to use the quota of biological samples that were put in long-term storage for possible future use, the research group agreed and explicitly stated in all the documents (the protocol, the information sheet and informed consent form) that a new consent from the subjects from whom the data and materials came will have to be requested.

Based on the information illustrated in the paragraph "Italian framework: no laws and guidelines for non-clinical observational studies", the epidemiological protocol was submitted to the Regional Ethics Committee for Clinical Trials of the Tuscany Region. The documents were submitted at the beginning of February 2021 and received ethical clearance at the beginning of May 2021. This was an important result, which could become a point of reference for other epidemiological studies based on a participatory approach. At the same time, this experience provided an opportunity to enrich the scientific debate concerning the adequate ethical evaluation process for studies in the non-clinical research field. Indeed, it is worth noting some problems that stemmed from submitting a participatory aetiological observational study to an Ethics Committee for clinical research that was set up to evaluate clinical studies which involve clinical trials.

Firstly, all the documentation to be completed for submission was tailored to meet the needs and requirements of patients who would be assigned a treatment in an experimental trial. For instance, the clearance form contained a specific request to provide the date of notification regarding the recruitment of patient number one disregarding the fact that no patients were actually involved, but only healthy people. Moreover, there was no request for any notification of the date of the interviews and collection of biological samples of all participants.

Secondly, under the current Italian norms, biomonitoring and the storage of human biological specimens are treated as an "experimental medical intervention". This means that the act of obtaining a biological sample is equated to the act of administering an experimental treatment, although the two acts are descriptively different and may have a deeply diverse impact in terms of possible risks and benefits on the health and psychological condition of the individuals concerned. Consequently, the improperly assigned equivalence of these two acts meant that, instead of stipulating an adequate assurance based on the actual entity of the possible risk, much higher insurance costs had to be paid, which had an impact on the overall research budget.

Thirdly, the research group – researchers and citizens – initially had some difficulty in receiving clearance, because the submitted epidemiological study was an independent study conducted by lay people and academic researchers not employed by the Italian National Health Service (NHS). These two conditions – i.e., the participatory nature of the study which means a co-responsibility of researchers and lay people and the non-belonging of researchers to the NHS – meant that the Ethics Committee would have had to adopt different criteria to establish whether the study met all the quality and ethical requirements of an epidemiological research project.

Indeed, in Italy, the principal investigator is usually a professional researcher or a medical doctor, not a lay person, which is the only person responsible for the study. In addition, Ethics Committees for clinical research are accustomed to evaluating two types of submissions: **1.** for-profit clinical trials; **2.** no-profit clinical research conducted by the regional health service.

Therefore, ethical approval procedures generally presume that a health service or a health public agency will be involved when a protocol is submitted for ethical clearance. To address these difficulties, the procedure of ethical evaluation was discussed with the Scientific Secretariat of the Regional Ethics Committee (Tuscany Region), which is a consulting body for the Ethics Committee for Clinical Trials of the Tuscany Region. After three months following the initial submission, the epidemiological study protocol and related documents received ethical clearance with the following new aspects accepted compared to the traditional ethical evaluation process:

- Firstly, the promoter of the study is a no-profit Small and Medium Enterprise (Epidemiologia&Prevenzione).
- Secondly, the principal investigator of the study is a general practitioner engaged by the promoter, i.e., Epidemiologia&Prevenzione.
- Thirdly, together with those of the researchers, the names of some citizens and some local health professionals who co-designed the study protocol and related documents are indicated as co-proponents of the study protocol.
- Fourthly, the full outpatient clinic set up and dedicated to the epidemiological study, with its own clinical lab and freezer, is an integral part of the surgery of the general practitioner who is the principal investigator of the study. These dedicated rooms and furniture are physically separated from the general practitioner's surgery to ensure the differentiation of the research activity from the health assistance provided in the surgery.
- Fifth, new information is described in the study protocol and the related information sheet, and informed consent form concerning the active role of citizens. For instance, the co-creative nature of the study and, consequently, the fact that citizens would be involved during all phases of the research was clearly stated. Specific training for citizens enrolled as active participants was envisioned (and then implemented). Namely, the standard training of staff in any epidemiological study plus specific training in research ethics and biobanking. Disclosure of possible financial and/or non-financial conflicts of interest by citizens who appear as co-proponents of the study was indicated.

The first, second, and fourth aspects were introduced in the documentation of the study following consultation with the Ethics Committees mentioned above, whereas the third and fifth aspects had already been introduced in the documentation at the time of the study protocol submission.

CONCLUSIONS

In the light of the historical scenario of the COVID-19 pandemic, the considerations and lessons learned that are illustrated in this paper may appear even more relevant. As some authors recently highlighted,[31,32] in a period when scientific data is changing rapidly, and research subjects are strongly influenced by the news circulating in the society they live in, it is difficult to organize and carry out clinical trials. Hence, the real-world evidence and the need to involve citizens actively becomes essential. Consequently, the awareness of the ethical aspects of the different types of studies and the elaboration of adequate paths for their ethical clearance process becomes crucial.

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