Annals of Research in Oncology
Vol. 3(4), 142-146, 2023

EDITORIAL

PRIVACY AND RETROSPECTIVE OBSERVATIONAL RESEARCH: A GUARANTEE, NOT AN OBSTACLE!

Gualberto **Gussoni** [1], Francesco **Dentali** [2], Carmine **Pinto** [3], Dario **Manfellotto** [4]

[1] Clinical Research Department FADOI (Italian Scientific Society of Internal Medicine), Milan, Italy
[2] Department of Medical Area ASST, Settelaghi, Varese, Italy. Department of Medicine and Surgery, Insubria University, Varese and FADOI, Rome, Italy
[3] Oncology Unit, Arcispedale S. Maria Nuova and FICOG (Federation of Italian Cooperative Oncology Groups), Reggio Emilia, Italy
[4] Internal Medicine, Isola Tiberina Hospital Gemelli Isola and FADOI, Rome, Italy
* Correspondence to: gualberto.gussoni@gmail.com, https://orcid.org/0000-0003-3573-5069.

Doi: 10.48286/aro.2023.79

Key words: *privacy; retrospective observational studies; Italy; consent; impact assessment.*

Received: Sep 12, 2023/**Accepted**: Dec 12, 2023
Published: Dec 22, 2023

Observational clinical studies are of growing importance, playing an increasingly complementary role alongside interventional research: the value of observational studies, supported by real-world data, is to provide scientifically useful information or, in some cases, comprehensive evidence that can help to orient clinical practice.

Retrospective observational studies, in particular, comprise collection and analysis of data from already existing medical files in hospitals/medical practices – *i.e.*, data concerning clinical testing and/or treatment that has already occurred. The possibility of relatively speedy (and uncostly) data collection for large numbers of patients, over what may even be long periods of observation, is among the distinctive features and chief strengths of this type of research.

Data processing for observational research has been, and continues to be, subject to close institutional and scientific attention: this is a field where regulatory compliance, above all for retrospective studies, can prove complex and entail numerous grey areas.

In Italy, the regulatory framework for processing of healthcare personal data features many different sets of requirements, unfortunately not always well aligned with each other: these include regulations issued by the European Union (EU Regulation 679/2016 - General Data Protection Regulation/GDPR), or by the national authorities (Legislative Decree 196/2003, complemented by Legislative Decree 101/2018 on data protection – "*Codice Privacy*"), as well as the specific requirements of the National Data Protection Authority (DPA)/*Autorità Garante per la protezione dei dati personali* – particularly those introduced during the past 15 years.

Many different issues, of a technical or a legal nature, have prompted debate regarding processing of healthcare data for research purposes. These include applicability of the legal concept of "legitimate interest", as well as the required conditions in order to ensure that "anonymisation"/"pseudonymisation" of data is guaranteed. In the specific case of observational research, significant considerations are i) the

clearly recognised ethical implications of its definition as "scientific" in nature, rather than "clinical-experimental"; ii) the applicability of Article 110 *bis* as the relevant source within the *Codice Privacy* (processing of personal data for scientific or statistical purposes, often ignored by the DPA), rather than Article 110 (regarding medical, biomedical and epidemiological research); iii) and the conditions related to secondary or "further" use of data. The last of these considerations is relevant when data collected in complete or ongoing clinical records, with a view to a primary aim (diagnostic/therapeutic purpose), are extracted for a secondary purpose (research).

The central concerns in retrospective observational research are patient consent and related criticalities, with particular reference to the difficulty of providing information and obtaining consent in the absence of direct face-to-face contact: this issue is obviously all the more critical in the case of deceased patients or those whose whereabouts are unknown.

As early as 2008, the Italian DPA underlined the principle that, for purposes of lawfulness, data processing within a retrospective observational study must be subject to the patient's prior consent, which must be informed and freely given. This concept has been recently reiterated, and in some respects reinforced, by a ruling of the DPA (dated 30 June 2022). Specifically, this was in response to a request regarding the creation of a database as an essential requirement for the conduct of research activity in accordance with a range of different protocols. The DPA authorised use of the database in question for the collection and storage of data on the basis of initial consent, subject to study sponsors subsequently obtaining further specific consent from the patients for implementation of individual projects (what the DPA calls "consent in progressive steps").

The difficulty of complying with this requirement, whether in for-profit or not-for-profit/academic research, can understandably be a significant deterrent to promotion of retrospective observational research, obviously leading to missed opportunities in terms of scientific progress and knowledge acquisition. However, implementation of the one-time consent strategy proposed by research organisations to address this difficulty cannot currently be considered a realistic prospect: this would mean that the patient's initial authorisation, at the time of data collection by the healthcare facility for purposes of treatment, or prior to inclusion in a new study, would also cover subsequent use of the data concerned for purposes of scientific research. Though the GDPR (see Whereas Clause n. 33 and Article 28) is partly open to such a possibility, a significant obstacle in this respect is the principle of "determined purpose", requiring that the specific objective of data processing must correspond to the information provided as part of the informed consent.

Italy's national DPA, both through the systematic renewal of its general authorisations from 2012 to 2016 and by means of a more recent provision (*Provvedimento* n. 146/2019), has nevertheless recognised that ex-post consent collection can entail a range of issues. These can be related to ethical concerns (e.g., when the person concerned is unaware of his/her condition and the information provided in relation to the project could trigger an alarm, or cause material or psychological damage), to personal incapacity (where the severity of the person's clinical condition allows them neither to understand the information provided nor to give proper informed consent, and they have no legal representative), or to organisational/methodological considerations (not taking into account data from subjects who are unavailable for informed consent could have significant consequences for the study, engendering alteration/bias of results). It is essentially on these concerns that Article 110 of the *Codice Privacy* is based, stating as it does that the informed consent requirement can be waived where the information concerned can be given, if at all, only with disproportionate effort, or in such a way as totally to impede or seriously jeopardise the achievement of the research aims. Where such conditions obtain, the data controller must: (1) adopt appropriate measures to safeguard the rights, freedoms and legitimate interests of the persons concerned; (2) obtain the approval of the Ethics Committee; (3) consult the DPA beforehand, in accordance with Article 36 of the GDPR.

The last of these requirements, considered mandatory by many Italian Ethics Committees and Data Protection Officers, is a further criticality. The reason for this is that it entails yet another unknown quantity that must be factored into the implementation of the study, for two reasons: the considerable time likely to elapse before the DPA's decision; and the rule, enshrined in article 110 *bis* of the *Codice Privacy*, that the absence of any ruling from the DPA within 45 days constitutes a rejection. Many legal experts and researchers are, like us, of the opinion that the requirement for the DPA's prior approval should not be automatic. The rationale for opposing this automatic requirement is twofold, since it is consistent neither with a detailed reading of Article 36 of the

GDPR (which identifies prior consultation with the DPA as a responsible choice of the data controller) nor with the principle of accountability on which the GDPR is largely predicated.

According to the principle of accountability, it is up to the data controller to determine whether impact assessment, with due consideration of data processing risks and security measures, leaves a level of risk for subjects' rights and freedoms that justifies triggering the requirement for prior consultation with the DPA. In practical terms, the impact assessment is aimed at identifying conditions in which a "high" risk exists, the remaining conditions being consequently defined with "not high" risk. Examples of studies with putative high risk can be considered those that include genetic data, or that concern particularly vulnerable populations (e.g. minors suffering from rare diseases), or that involve the circulation of data in non-European countries with lower levels of protection in terms of privacy. In addition, according to article 110 *bis* of the *Codice Privacy*, authorisation can also be given through general provisions of the DPA, adopted *ex officio* (and published in the Official Journal of the Italian Republic*/Gazzetta Ufficiale della Repubblica Italiana*). In our opinion, a general provision of this sort could be the above-mentioned *Provvedimento* n. 146/2019, recognising that data processing for purposes of scientific research is to be considered as legitimate even without the informed consent of the person concerned, subject to the conditions envisaged (ethical considerations, personal incapacity, organisational considerations). In all such cases, *Provvedimento* n. 146/2019 lays down the following requirements: (1) the existence of a study protocol; (2) the authorisation of at least one Ethics Committee; (3) exclusion of genetic data; (4) application of appropriate security measures and pseudonymisation techniques; (5) the undertaking to seek the patient's consent subsequently, in the event of their returning to the healthcare facility or reacquiring full possession of their faculties. In addition, where the impediment to consent stems from the patient's incapacity and from organisational difficulties, the DPA requires that (6) the patient's inclusion in the study without informed consent is to be considered an exceptional alternative to their enrolment with consent. Accordingly, it is required that a record be kept of all attempts made to trace deceased and/or missing subjects, and incapacitated subjects' legal representatives (though no precise indications are given regarding the means to be used for any such search).

The above indications show that retrospective observational studies are situated in a complex setting, combining a range of needs: ex-post, study-specific consent collection; data management for missing and/or deceased subjects; the requirement for prior consultation with the DPA, whether triggered or waived (mainly for reasons of time); the possibility for enshrining the principle of accountability in this process; and an impact assessment, to be drawn up by the data controller/study sponsor. The impact assessment should ideally be a mandatory feature of every clinical study (above all for large-scale studies), with a systematic description of how the data will be processed, evaluation of the risks for the rights and freedoms of the subjects concerned, as well as the measures (both technical and organisational) to address/mitigate these risks. For example, it is advisable to schedule different procedures for processing of genomic and molecular data from analysis of biological samples: somatic alterations, significant as diagnostic and/or prognostic factors and/or as therapeutic targets, are not considered to be high-risk items, whereas germ cell alterations are.

Italian researchers experience significant uncertainty regarding the correct conduct of retrospective observational studies, with specific reference to the related data processing requirements. To analyse ongoing issues, offering a practical tool and an operational guide with a view to promoting greater uniformity of approach in this respect, FADOI (Italian Scientific Society of Hospital Internal Medicine) has promoted the drawing up of a document that has recently been presented to the institutions concerned. This document brings together contributions from experts in the legal, scientific and ethical fields, as well as from representatives of Patients' Associations. **Figure 1**, below, provides a schematic overview of the operational proposals contained in the document, in the form of a flow diagram that can be readily consulted by investigators/study sponsors in search of guidance for data processing in the context of a retrospective observational study.

To note, the Italian *Centro di Coordinamento Nazionale dei Comitati Etici* (CCNCE - National Coordination Center of Ethics Committees) has released on 6 April 2023 a document entitled "*Criticità etiche e normative nel trattamento dei dati personali sanitari nella ricerca osservazionale* / Ethical and regulatory critical issues in the processing of personal health data in observational research". Point #9 of this document is dedicated to the proposals, which appear orient-

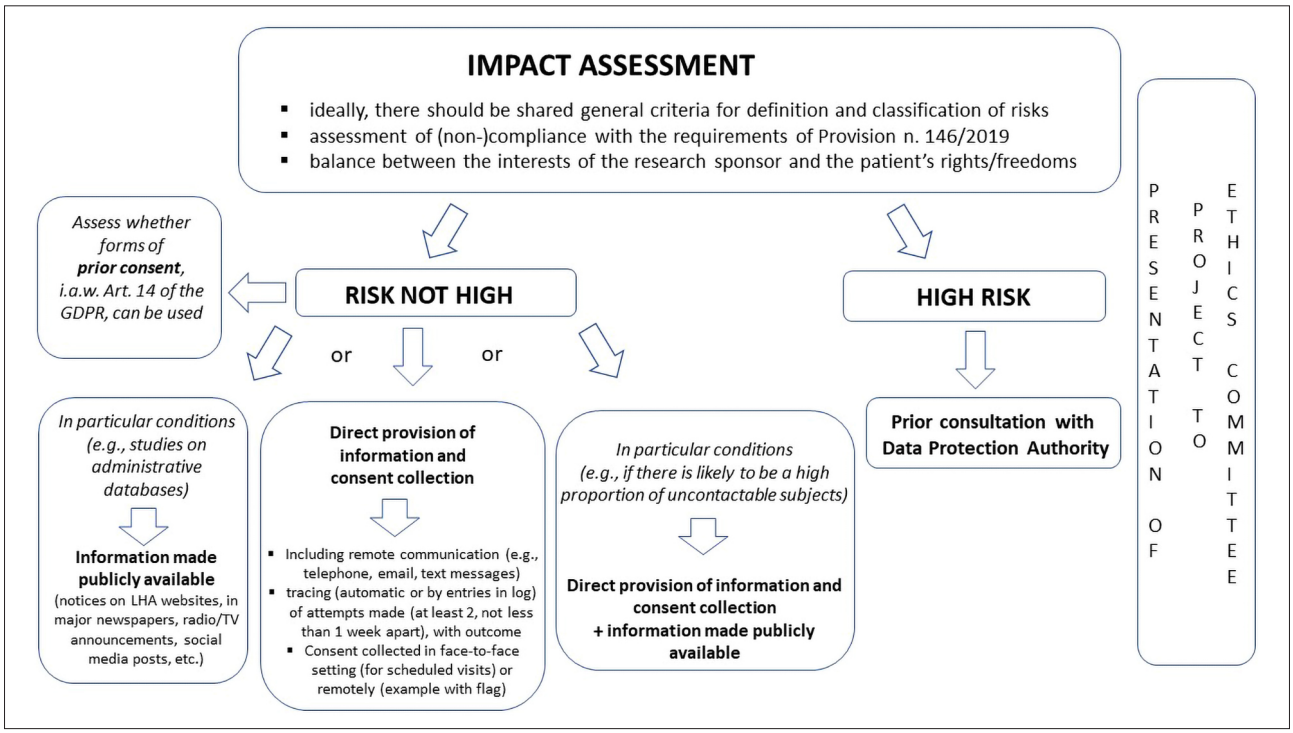

Figure 1. *Flow diagram for data processing in retrospective observational studies, with possible involvement of deceased and/or missing patients.*

ed towards a longer-term perspective than those described in our paper (and this is understandable taking into account that the CNCCE is an institutional body). However, the emphasis on the critical issues and the general attitude of the proposals in this document seem coherent and consistent with our indications. In addition, at the best of our knowledge, at least a couple of working groups are active on this topic in Italy, but up to now no publications or public results have emerged.

In conclusion, a key characteristic of retrospective observational research is that it can prove a timely source of real-world, real-life input to medical practice: such research therefore plays an increasingly important role, not only from a medical/scientific/clinical viewpoint, but also in an epidemiological/organisational perspective, and thus in terms of public health. The related opportunities are particularly important in a country like Italy, whose National Health System provides universal cover. In terms of personal data processing, however, the Italian scenario is more complex and challenging than that set out by the European Union in the GDPR, or that which prevails in some other countries. In particular, a substantial heterogeneity of decisions among different Ethics Committees and different Data Protection Officers has been often experienced. It is not easy to hypothesize how this heterogeneity can be overcome. One possibility could be represented by the publication of a clearer provision / guideline by the DPA, or of a Code of conduct approved by the same Authority, in order to clarify the interpretative scope of the articles of the *Codice Privacy* which are generating the critical issues covered by this paper. Finally, a further option could be a timely definition, by the DPA, of the so called provision "*Misure di Garanzia*", as provided for by the Legislative Decree 101/2018. The reasons of this critical situation are probably multiple: among them, on the one hand, the fact that the topic of observational clinical research is not among the priorities of the DPA, on the other hand the world of research has not been able to pursue this topic at an institutional level in a convinced and convincing manner, and with clear and unambiguous proposals. Hence the urgent need to ensure that, in Italy too, clear and straightforward procedures can be adopted for retrospective observational research: these should be as user-friendly as possible for patients, researchers and study sponsors alike, making regulatory implementation sustainable and underscoring the principle of the data controller's/study sponsor's accountability. By guaranteeing a correct balance between safeguards for the rights of the subjects concerned and the legitimate interest of the data controller/study sponsor, an enhanced regulatory framework would enable retrospective observational research to fulfil the value it can offer to society at large.

COMPLIANCE WITH ETHICAL STANDARDS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The Authors have declared no conflict of interests.

Authors' contributions

All Authors contributed to the drafting and critical revision of the article.

Ethical approval

N/A.

Publication ethics

Plagiarism

N/A.

Data falsification and fabrication

N/A