Special issue

The ethics of observational/epidemiological research conducted within the Covid-19 pandemic: implications for informed consent

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ABSTRACT: In observational research we observe what happens in the real world, and particularly in clinical practice. Contrary to what happens in clinical trials, there is no randomization. While clinical trials are governed by a precise and detailed regulatory framework, for observational research there are no specific regulations (except for the protection of personal data), and reference is made only to guidelines, codes and soft law. Consequently, in the absence of specific regulatory references, ethics committees frequently evaluate observational studies by applying the criteria that apply to clinical trials. This leads to inappropriate weighting and stiffness. To counter the Covid-19 pandemic, measures have been adopted to facilitate research, including observational research. Some provisions are also particularly relevant for information and consent, both for clinical practice and for the protection of personal data. These exceptional measures taken during the pandemic deserve attention: limited to some parts, they could be adopted not only in the emergency context of the pandemic, but also in ordinary situations.

KEYWORDS: Covid-19; epidemiology; ethics committees; informed consent; observational research

SUMMARY: 1. What are observational studies – 2. Classification of observational studies – 3. Why observational studies are important – 4. Critical Aspects in the use of Real World Data – 5. The definition in Italian legislation – 6. The regulatory profile in Italian legislation 7. Programmatic Document on Observational Research – 8. Observational studies and informed consent in the COVID-19 pandemic – 9. Exceptions to consent for the processing of personal data in the context of studies concerning Covid-19 – 10. To (not) conclude.

1. What are observational studies

The so-called "observational studies" use data obtained without any additional therapy or monitoring procedure beyond what happens in clinical practice. Observational research may involve the collection of data referring to a specific time (cross-sectional studies), or already available because they relate to previous situations or to the history of the subjects

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(retrospective studies) or generated through an observation projected over a time to come (prospective studies)[1]. The routinely collected medical data include healthcare claims, electronic medical records (EMRs) and patient registries, data collected from healthcare applications in mobile phones and wearable devices and others.

Therefore, a study is defined as "observational" if the decision to expose the individual patient to the medical procedure of interest is completely independent of the decision to include this patient in the study, that is, it is independent of the control of the researcher. In such cases, the exposure can be defined as "passive", in the sense that it is not actively defined by the study protocol.

However, in all cases in which the decision to expose the individual patient to predefined exposure is taken by the researcher (even indirectly, for example by relying on a randomization process), the study is classified as "experimental". The exposure, in fact, is of an "active" type, that is actively defined by the researcher through the study protocol.

Observational research can concern all areas of health, and in particular:

- diseases, health risk factors and other health-related events in the population (epidemiological studies);
- health interventions performed in clinical practice and not determined by the study design itself, including evaluations relating to their safety, efficacy and costs;
- care burden of diseases and of the various diagnostic and therapeutic pathways;
- aspects relating to lifestyles and quality of life.

William J Cochran, who was attributed with the expression "observational study", in 1965 defined an observational study as an empiric study in which: "the objective is to elucidate cause-and- effect relationships [in which] it is not feasible to use controlled experimentation, in the sense of being able to impose the procedures or treatments whose effects it is desired to discover, or to assign subjects at random to different procedures"[2].

2. Classification of observational studies

Observational studies can be classified according to several criteria.

A first classification criterion is based on the study question. Based on this criterion, studies can be "descriptive" or "analytical".

The study is defined as "descriptive" when its primary objective is the description of exposure to the medical procedure or the outcome.

The study is defined as "analytical" when its primary objective is to measure the association between exposure and the onset of the outcome, possibly inferring the causal chain that explains the process of interest.

Obviously, all experimental studies are by definition "analytical", as they investigate the effect of exposure to an intervention on a clinical outcome.

[1] E. DeRenzo, J. Moss, *Writing clinical research protocols. Ethical consideration*, Burlington (MA), 2006, 290-291.

[2] W. G. Cochran, *The planning of observational studies of human populations (with Discussion)*, in *Journal of the Royal Statistical Society*, A128, 1965, 134-155 OS, PM.

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A second classification criterion is based on the "exposure-outcome" timeline with respect to the start of data collection. Based on this criterion, studies can be "prospective", "cross-sectional" or "retrospective".

The study is defined as "prospective" in two cases:

- When the beginning of the exposure of interest coincides with the moment of enrolment of individuals in the study.
- When individuals, although already having had past exposure, have not yet developed outcomes and therefore have not yet been placed under observation.

The study is defined as "cross-sectional" when the exposure and outcome are assessed jointly, at the time of enrolment of the subject in the study. This is the typical case of prevalence studies.

The study, on the other hand, is defined as "retrospective" when, at the start of the study, the eligible individuals have already experienced exposure to the medical procedure and the clinical outcomes have already occurred.

A third classification criterion is based on sources. These can be primary or secondary.

Primary sources are characterized by the direct involvement of the individuals included in the study by the researcher. This is the case, for example, of data collection through a specially designed electronic folder.

The study, on the other hand, is based on secondary sources if the data are collected for reasons other than those directly related to the question under study. Retrospective observational studies use, with some exceptions, secondary sources.

3. Why observational studies are important

Observational studies are particularly important for the evaluation of both medical interventions and health care.

For the *evaluation of medical interventions*, the randomized controlled clinical trial (RCT) is considered, by the scientific community and the regulatory framework, as the most reliable method to generate credible evidence on the effectiveness of medical interventions, and in particular of pharmaceutical products. For several years, however, there has been widespread awareness that RCTs are not sufficient to guide the decision-making process as they are intrinsically unsuited to capture the impact of treatments in current clinical practice[3]. The complexity of therapeutic regimens, the demographic and clinical heterogeneity of patients receiving treatments, and the long period of many treatments, the often fragmentary adherence of patients to medical advice, explain the gap between the evidence generated in the controlled, but artificial, setting typical of the RCT, and its effective generalizability in the real world.

For the *evaluation of health care*, the typical approach is "service-centered", that is, it has as its observation unit the individual provider of services. The system for evaluating and comparing the performance of services dedicated to a single activity category is an irreplaceable governance tool for

[3] T. GREENHALGH. J. HOWICK, N. MASKREY, *Evidence Based Medicine: a movement in crisis?*, in *British Medical Journal*, 348:g3725, 2014.

the Health Service. However, this approach, although intrinsically useful to the decision-making process, has many critical aspects. In particular, it is not appropriate to evaluate the activity of each service as if it were independent from the activity of the others. In other words, a mosaic cannot be evaluated by evaluating each piece separately. In particular, in order to understand whether what is being done is useful, it is necessary to consider the entire care pathway.
Therefore, Real World Evidence, based on the past experience of patients in terms of treatments received and outcomes observed in the real world (and, therefore, on Real World Data), is able to produce credible evidence: it represents one of the fundamental pillars for both the proper treatment of patients, and the correct governance of interventions.

4. Critical Aspects in the use of Real World Data

For an effective and valid use of Real World Data it is necessary to adequately address some critical aspects relating to data, and in particular: the protection of personal data, the lack of homogeneity in organization, the possibility of access, adequacy.
The protection of personal data is particularly relevant for the purposes of informed consent and will be dealt with later in this text.
The lack of homogeneity in the organization of data depends in particular on the fragmentation of local, regional and national health information systems. Generally, they are independent from each other, have dissimilar organizations and structures, and use different information coding systems. The lack of homogeneity, in turn, exacerbates the difficulty in accessing data.
The possibility of accessing research data is not only recommended by national institutions, but it is often provided for through binding provisions. For example, it is recommended by the WHO Statement on Public Disclosure of Clinical Trial Results[4] and constitutes a particularly important element in the context of Regulation (EU) 536/2014 on clinical trials[5], and is binding for all Member States of the European Union.
With regard to the adequacy of the data, it must be considered that the majority of secondary sources of RWD are designed and fed mainly for reasons other than clinical research: for example, they are aimed at managing healthcare reimbursement (DBA), monitoring prescriptive appropriateness, the management of patients by general practitioners. Consequently, clinical research is, at most, a secondary use of RWD.
Critical aspects can be countered by implementing the recommendations set out in FAIR Guiding Principles for scientific data management and stewardship[6].
The FAIR (Findable, Accessible, interoperable, Reusable) principles are simple guidelines to ensure that systems can find and use data, facilitating its reuse.

[4] World Health Organization, *WHO Statement on Public Disclosure of Clinical Trial Results*, 2015.
[5] European Parliament, Council of the European Union, *Regulation (EU) 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, in Official Journal of the European Union*, L158, 27 May 2014, 1-76.
[6] M.D. Wilkinson, M. Dumontier, I. J. Aalbersberg, G. Appleton, M. Axton, A. Baak A, et al., The FAIR Guiding Principles for scientific data management and stewardship in Scientific Data 3, 160018, 15 March 2016.

However, the real challenge does not depend primarily on technology (that is, on our availability of tools for archiving and updating and analysing huge amounts of data), but rather on the use of robust observational plans and adequate methodologies of analysis, able to adequately consider the complexity of the phenomena and generate credible evidence.
Therefore, only correct acquisition and management of Real World Data will allow to generate valid evidence that can support the decision-making process. In this sense, big data is turning into smart data, that is data that make possible the taking of accredited decisions.

5. The definition in Italian legislation

The above relates to the methodology of observational studies.
There are some flaws in the definitions of "observational study" in Italian legislation.
Two in particular are highlighted here:

- the definition of "observational" applied only to studies in which a drug is used;
- the fact that any additional diagnostic observation (with respect to normal practice) makes the study "experimental".

As regards the restriction of the "observational" category to only studies in which a drug is used, already in the first regulatory framework of observational studies, dating back to the circular of the Ministry of Health of 2 September 2002, the term "observational" is used to refer to "the study focusing on problems and diseases in which medicines are prescribed in the usual way in accordance with the conditions set out in the marketing authorization. The inclusion of the patient in a specific therapeutic strategy is not decided in advance by the trial protocol but is part of normal clinical practice and the decision to prescribe the medicine is completely independent from that of including the patient in the study"[7]. The same circular defines the "observational study" as "non-interventional experimentation". The expression seems an oxymoron: every experimentation, by definition, involves an intervention.
A similar definition of "observational study" is found in legislative decree no. 211 of 24 June 2003: "non-interventional trial (observational study)": a study where the medicinal product(s) is (are) prescribed in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data"[8].

[7] MINISTERO DELLA SALUTE, *Circolare n. 6 del 2 settembre 2002, Gazzetta Ufficiale della Repubblica Italiana – Serie Generale*, 12 settembre 2002, 214.
[8] REPUBBLICA ITALIANA, *Decreto legislativo 24 giugno 2003, n. 211. Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico, in Gazzetta Ufficiale della Repubblica Italiana – Serie Generale*, 184, supplemento ordinario n. 130, 9 agosto 2003.

With the AIFA Resolution of 20 March 2008, guidelines were then provided for the categorization, authorization and conduct of observational studies, always limited to drugs[9].

Since the beginning of the Covid-19 pandemic, various measures have been adopted to facilitate the authorization and execution of studies, including observational studies, specifically concerning the emergency situation. Also in these measures it is confirmed that "in order to define a study as observational it is necessary that the prescription of the drug or drugs in question is part of normal clinical practice, and that these drugs are used in the indications and/or durations of treatment and dosages approved by the regulatory authorities"[10].

Regarding the possible addition of diagnostic or evaluation practices with respect to the routine management of the patient, it must be pointed out that, from a methodological point of view, the observational nature of the study is not altered. This is the case, for example, with procedures aimed at allowing a more accurate diagnosis of a specific pathology or those aimed at evaluating certain biological characteristics of the subject.

Indeed, the fact that observational studies are aimed at investigating phenomena that occur in a real context (rather than an artificially predefined one as in RCTs) does not mean that researchers cannot equip themselves with additional tools to evaluate natural phenomena that they cannot control (just as the biologist uses a microscope or the astronomer a telescope to better observe natural phenomena that are infinitely small or distant).

For evaluation by Ethics Committees, such studies should be classified as "observational with additional diagnostic and evaluation procedures". Of course this is only acceptable if: the additional procedures are methodologically justified; their costs are not borne by the Health Service; adequate guarantees are given to the patient.

6. The regulatory profile in Italian legislation

With law no.3 of 11 January 2018[11] Italy began a regulatory process aimed mainly at the implementation of Regulation (EU) 536/2014. Although the Regulation concerns RCTs, the law also mentions observational studies, with the aim of promoting their execution. The law delegates the Government to adopt, within 12 months, one or more legislative decrees for the reorganization of the legislation on clinical trials (Article 1, paragraph 1), including a "revision of the legislation relating to non-profit clinical trials and observational studies, in order to facilitate and support their implementation" (Article 1, paragraph 2, letter n).

[9] AGENZIA ITALIANA DEL FARMACO, *Determinazione 20 marzo 2008. Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci*, in *Gazzetta Ufficiale della Repubblica Italiana – Serie Generale*, 76, 31 marzo 2008.

[10] AGENZIA ITALIANA DEL FARMACO, *Considerazioni in merito alla definizione dello standard di cura ("standard of care", SOC) negli studi clinici in pazienti COVID-19*, https://www.aifa.gov.it/-/considerazioni-in-merito-alla-definizione-dello-standard-di-cura-standard-of-care-soc-negli-studi-clinici-in-pazienti-covid-19 (last accessed June 14th, 2021).

[11] PARLAMENTO ITALIANO, *Legge 11 gennaio 2018 n. 3. Delega al Governo in materia di sperimentazione clinica di medicinali nonché disposizioni per il riordino delle professioni sanitarie e per la dirigenza sanitaria del Ministero della salute, in Gazzetta Ufficiale della Repubblica Italiana – Serie generale*, 25, 31 gennaio 2018.

The government put into effect the delegation law by adopting legislative decree no.12 of 14 May 2019[12]. According to it, the Ministry of Health, in turn, should have adopted a decree by 31 October 2019 aimed at "facilitating and supporting the implementation of non-profit clinical trials and observational studies". To date, this decree has not yet been issued.
In the meantime, awaiting the adoption of this decree, various proposals have been made, with the aim of providing the Ministry of Health with useful ideas for the adoption of the decree itself. In particular, various scientific societies, together with universities and institutions, have drawn up a "Programmatic Document on Observational Research"[13].

7. Programmatic Document on Observational Research

The Programmatic Document contains various proposals[14], and in particular:

- It recommends that the new regulatory instrument mandatorily regulates all types of observational research in the biomedical and health sectors (with or without the use of drugs).
- In order to promote efficiency and avoid the multiplication of opinions on the same topic, it proposes that observational studies should be evaluated by a single Ethics Committee acting at national level, chosen from time to time within a national list of Ethics committees accredited by the Ministry of Health for the evaluation of observational studies.
- It proposes that in observational studies diagnostic procedures for additional evaluation should be permitted for the purposes of the study, provided they do not alter current clinical practice. It recommends that the addition of these practices does not entail, from a regulatory point of view, the classification of the study as experimental. The additional procedures should be confirmed by the General Directorate of the facility. The subject should be informed and provide their consent. The attending physician should receive an information note and the costs of the additional procedures should not be borne by the National Health Service, nor by the subject. The additional procedures should not involve more than minimum risks.

[12] Repubblica Italiana, *Decreto legislativo 14 maggio 2019, n. 52. Attuazione della delega per il riassetto e la riforma della normativa in materia di sperimentazione clinica dei medicinali ad uso umano, ai sensi dell'articolo 1, commi 1 e 2, della legge 11 gennaio 2018, n. 3*, in *Gazzetta Ufficiale della Repubblica Italiana – Serie generale*, 136, 12 giugno 2019.

[13] 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), *Documento Programmatico sulla Ricerca Osservazionale*, https://simef.it/index.php?option=com_dropfiles&task=frontfile.download&&id=304&catid=63 (last accessed June 14th 2021).

[14] C. Petrini, G. Fiori, G. Gussoni, S. Cazzaniga, G. Corrao, R. Danesi, V. Lovato, D. Manfellotto, F. Mastromauro, A. Mugelli, *Observational Studies: scientific societies recommendations for a new Italian legislation to facilitate their execution assuring ethics and the highest standards of scientific and methodological quality*, in *Annali dell'Istituto Superiore di Sanità*, 56, 3, 2020, 257-259.

Procedures involving slight and unlikely risk should be approved by the Ethics Committee and covered by an insurance policy stipulated by the study promoter.

- It recommends a single form at national level, a national register of studies, a national register of accredited sources for observational research, adequate training of the promoters of observational studies on methodological, ethical, regulatory and operational aspects.

The proposals set out in the Programmatic Document intervene on aspects intertwined with other regulations, in addition to those specifically dedicated to observational research. In particular, the issue is intertwined with the regulations of Ethics Committees and with the legislation concerning clinical trials.

As regards Ethics Committees, the same law no. 3 of 11 January 2018 mentioned above provides for a reduction in their number (currently 89 in Italy), with the establishment of a total of 40 local Ethics Committees on national territory specifically delegated to the evaluation of clinical trials. To date, however, the ministerial decree establishing the 40 Ethics Committees (which was to be enacted by 30 April 2018) has not yet been adopted. Once the 40 local Ethics Committees have been identified, instead of abolishing the existing unconfirmed committees, these could be charged with assessing studies other than clinical trials. Among these Committees, those qualified to assess observational studies could be selected according to the proposal of the Programmatic Document.

As for the relationship between observational studies and clinical trials, the proposal regarding the additional diagnostic procedures set out in the Programmatic Document seems of particular relevance. Currently, any additional diagnostic procedure, even without risks, compared to current clinical practice, gives rise to classifying the study no longer as observational, but as experimental. This is often disproportionate because it imposes on the observational study restrictions foreseen for experimental studies. In order to avoid this situation, in accordance with what is proposed in the Programmatic Document, a list of additional admissible procedures could be provided without the study becoming interventional.

8. Observational studies and informed consent in the COVID-19 pandemic

Only a part of observational research, in particular epidemiological studies, conducted in the context of the COVID-19 pandemic, takes place within health facilities.

Observational studies in the course of a pandemic may involve citizens in their homes, in normal work activities, asymptomatic people, symptomatic people at home, patients in isolation, patients in intensive care, and others.

For some research conducted not in person (for example online questionnaires, focus groups on electronic platforms) the use of electronic consent may be admissible, provided that the consent itself is expressed through an "unequivocal positive act" in a manner in compliance with the legislation in force[15].

[15] GARANTE PER LA PROTEZIONE DEI DATI PERSONALI, *Doveri - Come trattare correttamente i dati. Consenso*, https://www.garanteprivacy.it/home/doveri (last accessed June 14th, 2021).

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The research that takes place face-to-face in healthcare facilities can involve patients and healthcare professionals with different possibilities of interaction and expression of informed consent.
In observational studies, by definition, there is no intervention: data are studied. For this reason, the consent to carry out the study and the consent to the processing of personal data are often intertwined (unlike what happens in interventional studies, where the consent to the study and the consent to the processing of data should be clearly separated).
The reorganization of health facilities implemented in order to deal with the emergency of the COVID-19 pandemic has also had substantial repercussions on the procedures for obtaining informed consent for research with patients suffering from SARS-CoV-2 infection. In fact, the pressures, timescales, logistical difficulties due to the containment of the contagion have made it very difficult for health professionals to comply with the standard procedures for collecting informed consent.
The situation of the Covid-19 patient has peculiarities that must be adequately considered, also in order to prevent the acquisition of informed consent from becoming merely a formal act.
In particular, patients in isolation are in a situation of great vulnerability, first of all due to the lack of contact with their family environment or friends and, secondly, to the safety conditions in which the health personnel have to work, that is, with protective devices that can also make personal recognition difficult. It should also be considered that in the phases of greatest emergency in a pandemic, health workers can be so overwhelmed by events to the point of having difficulty or it being impossible for them to relate to patients beyond strictly therapeutic interventions and treatments.
It is therefore necessary to outline procedures that, on the one hand, meet the needs of the healthcare personnel and the patients who face the emergency and, on the other, guarantee the ethical standards of research and patient protection.
Disclosure must be aimed as much as possible at identifying and communicating essential information to the patient, in particular: the observational nature and voluntary nature of the study, the objectives of the research, the possible presence of a sponsor and the protection of personal data.
Maintaining, in all this, the rigor and empathy necessary for adequate communication and understanding.

9. Exceptions to consent for the processing of personal data in the context of studies concerning COVID-19

Art. 40 of the law of 5 June 2020[16] establishes that:

- Limited to the period of the state of emergency, "in order to improve the ability to coordinate and analyze the scientific evidence available on medicines, AIFA (Italian Medicines Agency) can access all data from experimental trials, observational trials and compassionate therapeutic use programs for patients with COVID-19 ".

[16] PARLAMENTO ITALIANO, *Legge 5 giugno 2020, n. 40. Conversione in legge, con modificazioni, del decreto-legge 8 aprile 2020, n. 23*, recante misure urgenti in materia di accesso al credito e di adempimenti fiscali per le imprese, di poteri speciali nei settori strategici, nonché interventi in materia di salute e lavoro, di proroga di termini amministrativi e processuali, in *Gazzetta Ufficiale della Repubblica Italiana – Serie generale*, 143, 5 giugno 2020.

- The protocols of the observational studies on drugs are also preliminarily evaluated by the Technical Scientific Commission (CTS) of AIFA, which also communicates the results to the Technical Scientific Committee of the Crisis Unit.

In a document on "Data processing in clinical trials and medical research in the context of the covid-19 health emergency", the Italian Data Protection Authority provides that, if for specific and substantiated reasons (e.g. informing the subjects proves impossible or involves a disproportionate effort or is likely to seriously impair the achievement of the objectives of the research), "it is not possible to obtain informed consent for the processing of personal data, also from third parties, or where doing so risks seriously undermining the successful outcome of the research (e.g. when processing data relating to deceased patients or patients in intensive care units), the data controllers intending to process personal data exclusively in connection with clinical trials and the compassionate use of medicinal products for human use with a view to the treatment and prevention of COVID-19 are not required, under the legislation relating to the current emergency situation, to submit their research project and the associated impact assessment for the prior consultation of the Data Protection Authority as referred to in Section 110 of the Italian data protection Code"[17].

Although the Data Protection Authority claims to apply the exceptions only to "experimental studies and compassionate uses of medicinal products for human use, with a view to the treatment and prevention of the Covid-19 virus", rather than a literal reading of the aforementioned document of the Data Protection Authority, a reading which includes a wider variation of the notion of "experimental study" is to be preferred, in line with the General Authorization no. 9/2016 of 15 December 2016[18] (confirmed by the provision of 13 December 2018[19]). This provision, for observational studies for which it is impossible to obtain the informed consent of the interested party, authorizes the processing of personal data if the research project has obtained the favourable opinion of the competent territorial Ethics Committee expressly excluding the need for a prior assessment by the Data Protection Authority. The fact that the notion of "clinical trial" used by the Data Protection Authority is to be understood in a broader sense can be deduced from various elements, and in particular:

the Data Protection Authority applies this notion also to "data relating to deceased patients", who obviously cannot be the subject of clinical trials;

when referring to "personal data relating exclusively to experimental studies and compassionate uses of medicinal products for human use, for the treatment and prevention of the Covid-19 virus", "exclusively" must be understood as referring to the purpose of "treatment and prevention of the Covid-19 virus".

[17] GARANTE PER LA PROTEZIONE DEI DATI PERSONALI, *FAQ - Trattamento dati nel contesto delle sperimentazioni cliniche e delle ricerche mediche nell'ambito dell'emergenza sanitaria da COVID-19*, https://www.garanteprivacy.it/temi/coronavirus/faq#sperimentazione.

[18] GARANTE PER LA PROTEZIONE DEI DATI PERSONALI, *Autorizzazione 15 dicembre 2016. Autorizzazione generale al trattamento dei dati personali effettuato per scopi di ricerca scientifica (Autorizzazione n. 9/2016)*, in *Gazzetta Ufficiale della Repubblica Italiana – Serie generale*, 303, supplemento ordinario 61, 29 dicembre 2016.

[19] GARANTE PER LA PROTEZIONE DEI DATI PERSONALI, *Provvedimento che individua le prescrizioni contenute nelle Autorizzazioni generali nn. 1/2016, 3/2016, 6/2016, 8/2016 e 9/2016 che risultano compatibili con il Regolamento e con il d.lgs. n. 101/2018 di adeguamento del Codice*, 13 dicembre 2018, https://www.garanteprivacy.it/home/docweb/-/docweb-display/docweb/9068972.

In conclusion, it is reasonable to believe that, in the event of the impossibility of obtaining the consent of the interested parties, even observational studies pursuing the objective of "treatment and prevention of the SARS-COV-2 virus" are assured exemption for the entire duration of the pandemic emergency.

10. To (not) conclude

Observation studies and other qualitative methods of research are critically important to produce valid findings. They are useful in biomedical research as they are in social science research, but, as for any other methods, they must be appropriately applied.

The regulatory framework governing observational studies in Italy, as well as in other countries, currently covers only studies involving the administration of medicinal products. A streamlined and efficient authorisation process for all types of observational studies, including those without medicinal products administration, is urgently needed. Some simplifications and some new criteria should be adopted. In particular, it is recommended that each study protocol receives a single competent evaluation (with multi-site and nation-wide validity) and provides for the possibility, under certain conditions, of additional diagnostic procedures while maintaining the observational (and not experimental) nature of the study.

In emergency conditions, as during the Covid-19 pandemic, exceptions have been adopted in order to facilitate approvals of new studies and the processing of personal data. This made it possible to rapidly launch new studies. Similar procedures could also be adopted in ordinary situations. However, this should not to lead to a relaxation in the rigor of the scientific method and in the protection of the rights of research participants.