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# Research ethics during the COVID-19 pandemic: observational and, in particular, epidemiological studies

ISS Bioethics COVID-19 Working Group

Version of May 29, 2020



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## **ISS Bioethics COVID-19 Working Group**

Coordinator:

Carlo PETRINI

*(Head of the Bioethics Unit and President of the Ethics Committee, ISS, Roma)*

Components:

Luigi BERTINATO (Segreteria Scientifica della Presidenza, ISS, Roma); Giovanna FLORIDIA, Sabina GAINOTTI, Luciana RIVA (Unità di Bioetica, ISS, Roma); Alberto GAMBINO (Università Europea di Roma); Ignazio GRATTAGLIANO (SIMG e Università degli Studi di Bari); Donato GRECO (già Direttore Laboratorio ISS, Roma e Direttore Generale della Prevenzione Ministero della Salute); Gualberto GUSSONI (Direttore Scientifico FADOL, Roma); Chiara MANNELLI (Istituto di Candiolo, FPO-IRCCS, Candiolo, TO); Assunta MORRESI (Università degli Studi di Perugia); Pierantonio MUZZETTO (Università di Parma, OMCEO Parma, Consulta Deontologia Nazionale FNOMCeO); Federico NICOLI (Università degli Studi dell'Insubria, Varese e Domus Salutis, Brescia); Francesca PIERGENTILI (Ateneo Pontificio Regina Apostolorum, Roma); Giorgio RESTA (Università degli Studi Roma Tre)

## **Authors of this document**

Sabina GAINOTTI, Alberto GAMBINO, Donato GRECO, Gualberto GUSSONI,  
Chiara MANNELLI, Assunta MORRESI, Federico NICOLI, Giorgio RESTA, Carlo PETRINI

Translation by Julie Sawitzke.

Istituto Superiore di Sanità

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Biomedical research includes interventional or experimental research, and observational / epidemiological research. While the first types of research are governed by specific regulations, some of which are dedicated to the COVID-19 pandemic situation, for the latter there are no regulatory references except "soft law" documents. This report aims to offer references to researchers engaged in the study of SARS-CoV-2 and to the Ethics Committees (EC) engaged in the evaluation of observational / epidemiological research conducted in an emergency, starting from the literature and recommendations of International Organizations, relating to: values and principles of research ethics to be considered in the planning and evaluation of observational / epidemiological research in emergency COVID-19; role of the ECs and procedures to be adopted to respond promptly to requests for evaluation of observational / epidemiological research in the field of COVID-19 and non-COVID-19; specificity and exemptions from informed consent for observational / epidemiological research in COVID-19; collaboration between researchers and timely sharing of research results and data.

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For information: [sabina.gainotti@iss.it](mailto:sabina.gainotti@iss.it)

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# Preface

The Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy), as the technical-scientific body of the Italian National Health Service, has the task of promoting and protecting national and international public health through research, surveillance, regulation, control, prevention, communication, consultancy and training activities.

The topic addressed in this report “Research ethics during the COVID-19 pandemic: observational, and in particular, epidemiological studies” is crucial for the Institute. In fact, it includes two areas in which the Institute has a central role in the national landscape: 1) research, which yields the knowledge; and 2) actions, to counter the spread of diseases. The two areas are closely linked in order to plan and implement interventions aimed at fighting diseases.

With regard to research, the types of studies covered by this report are particularly relevant for the Institute. In fact, although it is also widely involved in the management of clinical trials (e.g., in the specific case of COVID-19, the randomized controlled national study to evaluate the efficacy and role of the plasma obtained from convalescent patients promoted by the Institute together with the Agenzia Italiana del Farmaco/Italian Medicines Agency), it has a central role in the collection, processing and analysis of data on the causes, course and consequences of diseases.

Observational research, and in particular epidemiological research, requires particular cautions in terms of ethics. Like all research, observational studies must respect rigorous scientific criteria: research must meet validity requirements (i.e., be methodologically rigorous) and value (i.e., be potentially useful for the advancement of knowledge). Value and validity are not, however, sufficient. Observational research must also meet ethical requirements.

A basic criterion in the ethics of biomedical research is the primacy of the interest of the individual participant over the interests of society. In observational research, and in particular epidemiological research, this primacy is generally absent; the main aspect is the advancement of knowledge for the benefit of all. This dimension, in which the common utility has the primacy over the interest of the person, does not imply that observational research does not conform to ethics, but that adequate precautions are needed to guarantee respect for persons.

With this report, we have tried to provide useful insights especially for the evaluation of observational studies that the Ethics Committees are called to evaluate. The ethical implications of observational research, however, are numerous and do not end in what this report covers. Further elements are found in other reports produced by the ISS Bioethics COVID-19 Working Group, including Rapporto ISS COVID-19 n. 34/2020 “Territorial surveillance and protection of public health: some ethical and legal aspects” and n. Rapporto ISS COVID-19 n. 42/2020 “Protection of personal data in the COVID-19 emergency”.

*Carlo Petrini*



# Premise

The COVID-19 pandemic has prompted researchers around the world to study SARS-CoV-2 and its consequences. New clinical and non-clinical studies of all kinds are continuously being launched.

Clinical trials involving COVID-19 are regulated by specific standards.

Other types of studies, however, are not governed by a specific and detailed regulatory framework, and for these we refer mainly to so-called “soft law” documents such as declarations, codes of ethics, conventions, guidelines and others.

In the absence of specific regulations, there is often a tendency by researchers and Ethics Committees (EC) to apply evaluation criteria for clinical trials to other types of studies. This can be a guarantee of rigor and protection for the persons involved, but it can also be an obstacle, to the detriment of research and of the persons themselves.

The emergency imposed by the pandemic is grafted on this situation. Exceptional circumstances call into question the entire regulatory-organizational structure. In emergency conditions, it is necessary to proceed as quickly as possible, by safeguarding, at the same time, both scientific rigor and compliance with ethical requirements. It is not a question of relaxing the rules, but of adopting methods that guarantee efficiency, efficacy and timeliness both in the evaluation of the studies by the EC and in the execution of the studies themselves.

There is no intention here to propose new operating standards for ECs and researchers to be applied in the context of a pandemic emergency: rules and procedures must be developed and adopted according to the appropriate institutional pathways. For the role and the field of competence that characterizes the ISS Bioethics COVID-19 Working Group, we want to propose some considerations with the hope that they can be of help to those who program, evaluate, perform or participate in research, for the purpose of a better classification in the pandemic emergency situation.

In drawing up these proposals, the Working Group has largely drawn on a vast collection of documents produced by authoritative institutions (Italian, other nations and international) on the subject of research ethics.

All this is introduced by a short scientific-methodological framework on the types of research. With it we also want to reiterate that the first requirement of ethics is scientific reliability, understood as the adoption of rigorous investigation methods, typical of scientific research.



# Introduction

The COVID-19 epidemic brings with it many unknown aspects that prevent us from responding effectively to the challenges posed by the event: prevention policies, timely diagnosis of new cases, the role of the genome in the development or not of symptoms, the efficacy of the therapies available in different types of patients, the organizational modalities of the health services in response to the virus, the level of acceptance of the isolation measures by the population, are all problems that require the acquisition of knowledge based on solid scientific evidence.

In an emergency context full of uncertainties, research is a real ethical imperative since, if research is not performed, the risk of adopting ineffective prevention measures increases, as well as offering inadequate or even harmful treatments to those affected<sup>1</sup>.

However, the same research activity always carries risks, and in health emergencies poses unique and important ethical problems<sup>2</sup>.

The health emergency is a particularly complex context in which the researcher must, on the one hand, obtain results in a short time, and on the other, maintain high quality standards so that decisions made on the basis of new knowledge are effective and not harmful.

The protections for research participants must be the same as those guaranteed under normal conditions, the studies must be scientifically sound, have social value and provide for a fair balance of benefits and risks for the participants<sup>3</sup>.

It is therefore important that:

- The values and principles of research ethics are considered in the design and evaluation of ongoing research, and individual and collective interests are adequately balanced;
- The EC can respond timely to new evaluation requests by adapting its standard operating procedures to the new reality, ensuring ethical protection and standards for all those involved in COVID and non-COVID research;
- Persons affected by SARS-CoV-2 infection, when they can freely express their consent, are adequately informed, among other things, of the voluntary nature of participation in research, of the observational nature and objectives of the research in which they participate, of any presence of commercial sponsors, and protection of personal data;
- The researchers promptly share the results of the research, whose quality is adequately controlled, with the scientific community, decision-makers, public health officials, research participants and interested populations, at both a national and international level, and subsequently make the data available for aggregation with other datasets and reuse in further research.

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<sup>1</sup> World Health Organization. *Guidance for managing ethical issues in infectious disease outbreaks*. Geneva: WHO; 2016. p 30-41

<sup>2</sup> World Health Organization. *Research ethics in international epidemic response. Technical consultation WHO Technical Consultation. Geneva, Switzerland 10–11 June 2009. Meeting report*. Geneva: WHO; 2010.

<sup>3</sup> Smith M, Upshur R. Pandemic disease, public health and ethics. In: Mastroianni AC, Kahn JP, Kass NE (Ed.). *The Oxford Handbook of public health ethics*. Oxford: Oxford University Press; 2018.

# 1. Types of research

In descriptive terms, research in the biomedical field is a preliminary distinction between pre-clinical research (research that is not conducted on humans, carried out in the laboratory) and clinical research (which is conducted on humans), which in turn has traditionally been divided into “Interventional (experimental) research” and “observational/epidemiological research”. It should be emphasized that for some specific types of study, this clear distinction between the two dimensions of clinical research is not always easily applicable.

The following are more specific details about the various types of research defined above:

- **Preclinical scientific research:** this is research aimed at identifying and designing clinical trials in humans (or even at understanding some processes or elements emerging from clinical trials). They are studies conducted in the laboratory: from molecular systems of interest, to biological materials and organisms of animal and human origin, to animal models. As far as the COVID-19 contagion is concerned, this type of study ranges from in vivo animal and in vitro virology to the development of diagnostic tools.
- **Interventional research (experimental):** this research involves the prospective assignment, random or otherwise, of individuals or groups to certain health-related interventions, drugs and biological products, devices and prevention programs (e.g. vaccines), and therefore require active intervention by the researcher. The most rigorous clinical trial model is the controlled randomized trial, in which the study intervention is compared with one or more interventions already available (“control”), and the assignment of the subject (or groups of subjects) to the different types of intervention is carried out randomly (“random”) (Figure 1). This ensures that factors other than interventions that could influence the results of the study are distributed equally among the subjects assigned to the experimental or comparison intervention. Non-randomized controlled trials are also possible (but not recommended due to the impossibility of carrying out the above guarantees), as well as uncontrolled studies, in which all the subjects eligible for the study receive the experimental intervention and the effectiveness of the intervention itself is reported in terms of absolute benefit (e.g. healing of 50% of subjects). Regarding COVID-19 infection, in Italy in the past weeks numerous experimental studies have been authorized which mainly concern drugs with anti-infective, anti-inflammatory/immunomodulating and antithrombotic / anticoagulant action<sup>4</sup>.
- **Observational/epidemiological research:** this research may cover areas of close clinical relevance (hospital and non-hospital) as well as the impact of social determinants or scientific evidence on health, or more administrative, social and economic aspects of health and healthcare. Unlike what happens in interventional research, these are investigations in which the assignment of the patient to a specific diagnostic / therapeutic / care strategy or exposure to a situation / risk factor are not conditioned by the researcher but fall within normal behavior or clinical practice, without applying procedures that may present an experimental character. This aspect, with reference to the COVID-19 emergency, was highlighted by a note from AIFA (Agenzia Italiana del Farmaco/Italian Medicines Agency) of 5 May 2020, in which it is specified that:

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<sup>4</sup> Agenzia Italiana del Farmaco. *Sperimentazioni cliniche - COVID-19*.

In order to define an observational study, it is necessary that the prescription of the drug or drugs under examination is part of normal clinical practice, and that these drugs are used in the indications and / or duration of treatment and dosages approved by the regulatory authorities<sup>5</sup>.

The **definition of “observational study”** in force in Italy dates back to the circular of the Ministry of Health 2 September 2002 which classifies as “observational”:

Study focused on problems or diseases for which the medicines are prescribed according to the indications of the marketing authorization. The assignment of the patient to a specific therapeutic strategy is not decided in advance by a trial protocol but is part of normal clinical practice, and the decision to prescribing the medicine is completely independent of that of including the patient in the study.<sup>6</sup>

The same circular defines “observational studies” as “non-interventional experimentation”, thus adopting an inappropriate expression because every experimentation, by definition, involves an intervention. A similar definition of “observational study” is found in decree no. 211, namely:

Study in which the medicines are prescribed according to the indications of the marketing authorization, the assignment of the patient to a specific therapeutic strategy is not decided in advance by a trial protocol but is part of normal clinical practice and the decision to prescribing the medicine is completely independent of that of including the patient in the study. No additional diagnostic or monitoring procedures are applied to patients, and epidemiological methods are used to analyze the data collected.<sup>7</sup>

With the AIFA Determination of March 20, 2008, guidelines for the categorization, authorization and conduct of observational drug studies were then provided<sup>8</sup>. Italian legislation therefore includes in the category of “observational studies” only studies in which there is a prescription for a medicine. There are, however, numerous other types of studies that use observational methodologies, but that do not involve prescribing medicines. In this report, specific reference is made to these types of study.

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 (retrospective studies), or generated through an observation projected over a time to come (prospective studies).

Observational research can have descriptive objectives (essentially in the preliminary stages of evaluating a phenomenon, such as in case series or in some cross-sectional studies) or analytical (for example in cohort studies or in case-control studies), in the presence of preliminary indications that allow the formulation of a hypothesis to be tested in research (Figure 1).

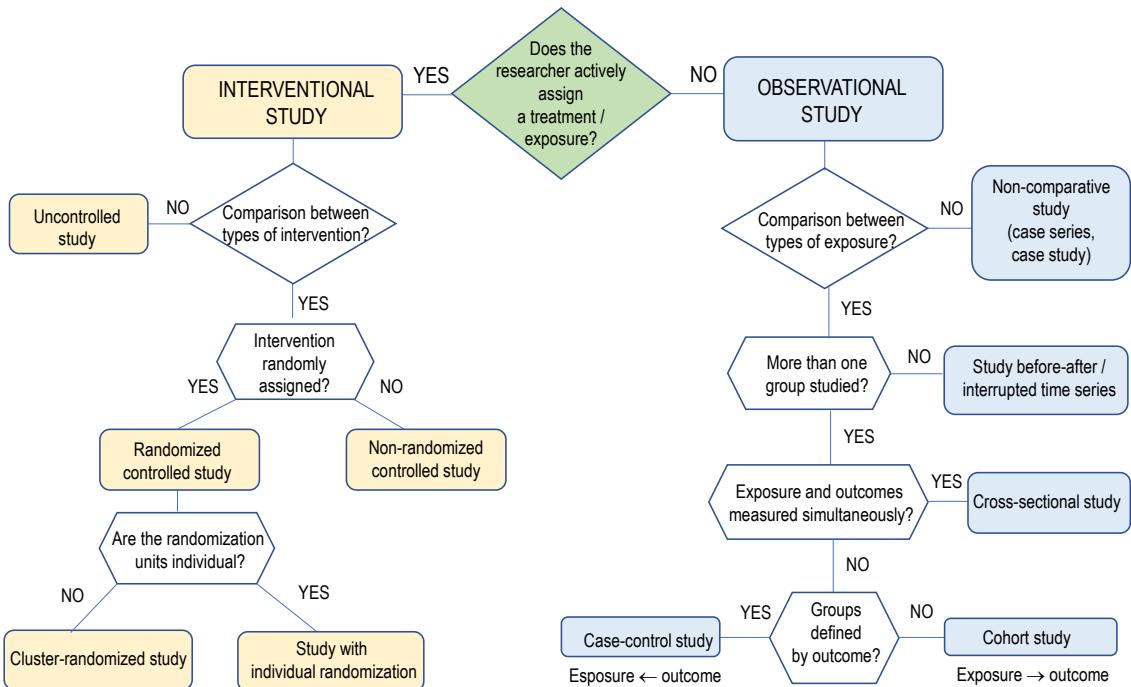
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<sup>5</sup> Agenzia Italiana del Farmaco. *Considerazioni in merito alla definizione dello standard di cura (“standard of care”, SOC) negli studi clinici in pazienti COVID-19*. Roma: AIFA; 2020.

<sup>6</sup> Ministero della Salute. Circolare n. 6 del 2 settembre 2002. *Gazzetta Ufficiale della Repubblica Italiana – Serie Generale* 12 settembre 2002, n. 214.

<sup>7</sup> Italia. 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. *Gazzetta Ufficiale della Repubblica Italiana – Serie Generale* 9 agosto 2003;184, supplemento ordinario n.130.

<sup>8</sup> Agenzia Italiana del Farmaco. Determinazione 20 marzo 2008. Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci. *Gazzetta Ufficiale della Repubblica Italiana – Serie Generale* 31 marzo 2008; 76.



**Figure 1. Classification of interventional and observational studies**

(Modified by Scottish Intercollegiate Guidelines Network. Guideline development process.

<http://www.sign.ac.uk/pdf/studydesign.pdf>)

In the context of observational research, epidemiological research studies the distribution and frequency of diseases and health-related events in the population, thus affecting individuals in contexts not only in hospitals but also on the territory, in the so-called "real life".

It is divided into:

- **Descriptive epidemiology:** studies the incidence and prevalence of health events in their distribution of time, space and person, and the presence of factors associated with them: for example, the distribution of COVID-19 cases by age and sex, by severity, and antibody seroprevalence studies.
- **Analytical epidemiology:** studies the risk factors and determinants associated with a given disease by comparing the cases exposed and not exposed to certain factors, including etiological research that investigates the real causes of a disease. For example, smoking and COVID-19 prognosis, other diseases and mortality from COVID-19, air pollution and COVID-19.
- **Evaluative epidemiology:** studies the impact of prevention or prophylaxis measures, treatments of populations, effectiveness of health services. For example, the impact of the closure of schools on mortality from COVID-19, the usefulness of masks to limit the spread of infection, the effectiveness of hospital-center or territorial approaches, the impact of vaccines.
- **Computational epidemiology:** studies epidemiological and mathematical models concerning the natural history of diseases, in an attempt to interpret their past, present and future. For example, the mathematical models on the spread of COVID-19.

- **Social epidemiology:** studies the differences in epidemiological patterns in relation to geographical differences, production characteristics of the territory, environmental factors, social and cultural elements, models of social and family aggregation.

Currently many of these types of research can make use of Big Data, that is, large aggregations of different administrative and demographic data collection systems connected by identification keys.

## 2. Ethical values in public health research

Public health has the fundamental objective of reconciling the interest and protection of the community with the protection of individuals. Even the ethics of public health research, given its emphasis on the collective dimension, requires a different balance between values compared to an ethics focused mostly on individual interests, in particular autonomy.

During a pandemic, public health researchers have important responsibilities in directing the responses of the community and must pay particular attention to collect quality data, avoid misinterpretations and rough statements, and clarify any misunderstandings regarding data and information. At the same time, the emergency condition makes it necessary to adapt work to new circumstances.

In an emergency situation the ethical dimension in public health research cannot be considered secondary for two reasons:

1. ethics offers criteria and principles for research and are always valid. These criteria and principles do not change in relation to the emergency context;
2. public health decisions have an important social value because they affect the health of a community and therefore also the ethos of a given population.

The American Public Health Association (APHA) Code of Ethics, among others, presents some values that allow us to better describe the responsibilities of those who work in public health, and the importance of a modus operandi that is always transparent and accessible to anyone<sup>9</sup>. Among these, there are:

- **Professionalism and trust:** The burden of guiding individual and collective choices in conditions of suffering and vulnerability requires great professionalism in those who decide on public health and trust by citizens, especially when scientific knowledge is lacking or inadequate. During the pandemic, researchers are called upon to promote a high level of research to increase knowledge in experimental and real life, and to share it as quickly as possible with the scientific community and the population.
- **Health and safety:** Defending the right to health care for all citizens is the basic prerequisite of our National Health Service (NHS), and research activities must not hinder or subtract resources from carrying out assistance activities. In particular, researchers have an ethical responsibility to promote valid and valuable research, and at the same time to guarantee the highest level of safety and health protection for all those involved.
- **Justice and equity:** Public health research presupposes an ethical obligation to use knowledge to promote a fair distribution of burdens and benefits, without discriminating against the vulnerable populations and combating unacceptable inequalities.
- **Interdependence and solidarity:** In the pandemic emergency, the health of each individual is interconnected with those of the community. Public health research also has an ethical obligation to emphasize how the interpersonal dimension (in its most diverse forms) influences the health of each individual. This entails enhancing the importance of a solidarity and reciprocity attitude for citizens, which is expressed among other things, in participation in research and, for researchers, in collaboration in wider research and in sharing data with other research groups.

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<sup>9</sup> American Public Health Association. *Public Health Code of Ethics 2019*. Washington, DC: APHA; 2019.

In Table 1 the values described above are presented together with those principles of bioethics most implicated. The effort to balance these principles allows the value implications in relation to the complex issues present in observational research to be analyzed more appropriately.

**Table 1. Ethical values and applications in observational research**

Ethical values	Applications in observational research
<b>Professionalism and trust (beneficence / justice)</b>	Quality and social value of studies involvement of participants in observational studies
<b>Health and safety (beneficence / non maleficence)</b>	Observational research in emergency conditions between advancement of knowledge and protections of participants
<b>Justice and fairness (justice / autonomy)</b>	Seeking the benefit of the whole population in respect of the rights of the individual, protection of vulnerable groups
<b>Interdependence and solidarity (autonomy / beneficence)</b>	Responsibility of individuals within the community, with particular reference to participation in research for citizens and collaboration with other groups for researchers

### 3. Role of Ethics Committees

ECs have a fundamental role in promoting the ethical values in research and in guaranteeing the methodological solidity and ethicality of observational studies and therefore the validity of the inferences that can derive from them.

When specifically addressing the evaluation of non-pharmacological observational research, particular attention should be paid to the risks implicit in such studies<sup>10,11</sup>.

In the context of the COVID-19 emergency and non-pharmacological observational studies, the individual risk for the subjects involved is limited to the sphere of personal data, while the risk for the community deriving from the adoption of health policies based on inaccurate data can be very significant in terms of avoiding mortality. ECs must therefore pay the utmost attention to the methodological quality of the studies, especially in evaluating projects that stem from the observation of very limited cases and without defined hypotheses to be verified.

In this sense, the condition of the pandemic emergency generates a possible double consequence: on the one hand, the need to quickly identify useful clinical or research ideas (hypotheses generating) can justify an accelerated data collection and on limited numbers; on the other hand, the risk that information obtained without appropriate planning (e.g. of the sample size) could lead to inappropriate choices with a very significant negative impact, especially in a situation in which errors and lost time are particularly harmful.

#### 3.1. Do non-pharmacological observational studies always have to be evaluated by an EC?

Observational studies, in particular epidemiological studies, require the collaboration of multiple research centres to collect data and evidence at the population level.

In the emergency phase, it can be asked whether observational studies, which do not entail physical risks for participants higher than normal clinical practice or daily life, should be assessed and approved by an EC and whether the assessment should be done by a single coordinating EC or even from multiple CE.

In Italy, the evaluation of non-pharmacological observational studies is not governed by the same normative references provided for the evaluation of clinical trials<sup>12,13</sup> and observational studies concerning drugs.<sup>14</sup> However, involving the processing of personal data, observational studies apply to: the provisions of the Regulation EU 2016/679 of the Code regarding the protection of personal data (in part. art. 110); at a

<sup>10</sup> See for example *MRC Guidance on managing risk in public health research* of the Medical Research Council.

<sup>11</sup> Rosmini F, Ferrigno L. Aspetti etici della ricerca epidemiologica. Roma: Istituto Superiore di Sanità; 2015 (Rapporti ISTISAN 15/44). p. 26-8.

<sup>12</sup> Europa. 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. *Official Journal of the European Union* 27.5.2014: L 158/1.

<sup>13</sup> Italia. 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. *Gazzetta Ufficiale della Repubblica Italiana – Serie Generale* n.25 del 31-01-2018 (Artt. 1-3).

<sup>14</sup> Agenzia Italiana del Farmaco. Determinazione AIFA 20 marzo 2008: Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci. *Gazzetta Ufficiale della Repubblica Italiana – Serie Generale* n. 76 del 31-3-2008.

more specific level, the provisions of the Data Protection Authority - in particular the General Authorizations n. 9/2016 on the processing of personal data for scientific research purposes and n. 8/2016 on the treatment of genetic data<sup>15,16,17</sup>.

However, it should be noted that, independently of the legislation, the evaluation and approval of research projects by an EC is required by various research funding agencies, as well as by the main scientific journals for the publication of the results<sup>18</sup>.

A possible difficulty in deciding the evaluation to which a project is subject relates to its definition as a "surveillance" or "research" activity.

The debate on whether to consider public health surveillance as "research" is still open and has significant practical consequences, including, in addition to the need for an assessment by an EC, the methods of patient / citizen participation (with or without the signature of the consent) as well as the legitimacy of an exceptional failure to acquire the consent itself.

The World Health Organization (WHO) defines surveillance activities as:

"The systematic and continuous collection, analysis and interpretation of health-related data necessary for the planning, implementation and evaluation of public health practices"<sup>19</sup>.

However, by adopting the definition of "research" used in the document "Ethical principles and guidelines for the protection of human subjects of research" (the so-called Belmont Report<sup>20</sup>), that is to say an activity "designed to develop or contribute to the development of generalizable knowledge", we must recognize that a large part of the surveillance activity falls within the research.

On a more general level, we could also say that everything related to public health is research: according to some authors one of the main functions of a public health system is "gathering health information and distributing such data for the well-being of the community". If we agree with the WHO that "all research with human participants is presumably subject to EC control", we must deduce that public health surveillance activities must also be assessed and approved by an EC before they can be started."<sup>21 22</sup>.

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<sup>15</sup> Garante per la Protezione dei Dati Personalini. Autorizzazione generale al trattamento dei dati personali effettuato per scopi di ricerca scientifica. (Autorizzazione n. 9/2016).

<sup>16</sup> Garante per la Protezione dei Dati Personalini. Provvedimento che individua le prescrizioni contenute nelle Autorizzazioni generali n. 1/2016, 3/2016, 6/2016, 8/2016 e 9/2016 che risultano compatibili con il Regolamento e con il DL.vo 101/2018 di adeguamento del Codice. Registro dei provvedimenti n. 497 del 13 dicembre 2018

<sup>17</sup> Italia. Decreto Legislativo 10 agosto 2018 n. 101. Disposizioni per l'adeguamento della normativa nazionale alle disposizioni del regolamento (UE) 2016/679 del Parlamento europeo e del Consiglio, del 27 aprile 2016, relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati e che abroga la direttiva 95/46/CE (Regolamento Generale sulla Protezione dei Dati). *Gazzetta Ufficiale della Repubblica Italiana Serie Generale* - n. 205, 4-9-2018.

<sup>18</sup> Committee on Publication Ethics. *Guidelines on good publication practice*. Eastleigh: COPE; 1999.

<sup>19</sup> World Health Organization. *WHO health topics | Public health surveillance*. Geneva: WHO; 2014.

<sup>20</sup> United States Department of Health and Human Services. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical Principles and Guidelines for the Protection of Human Subjects of Research. April 18, 1979.

<sup>21</sup> Prott DJ. The application of information science, information technology, and information management to public health. In: Detels R, McEwen J, Beaglehole R (Ed.). *The Oxford textbook of public health*. Oxford: Oxford University Press; 2002. Volume II, p. 417-44 (419).

<sup>22</sup> Petrini C. *Ethics in public health surveillance*. Ann Ist Super Sanita 2013;49(4):347-53.

As for the second problem, which ECs are responsible for the evaluation and approval of individual studies, the legislation does not give clear indications. There are proposals for their effective regulation in relation to the need for evaluation and approval by a single coordinating EC rather than by the EC of the individual participating centres<sup>23</sup>.

In addition to the approval by the EC, some non-pharmacological observational studies conducted in the territory, and especially in General Medicine, require authorization from the Local Health Authorities (*Aziende Sanitarie Locali*, ASL) and in some realities from the medical districts for the enrolment of patients. These steps delay and sometimes hinder the realization of the studies. In conditions of pandemic and therefore of high risk for the communities, some administrative steps could be abolished.

### 3.2. EC procedures in emergency COVID-19: some WHO proposals

In emergency situations, the ECs must optimize their procedures and establish adequate and flexible mechanisms, to avoid that the review and ethical evaluation process entails delays in launching useful research in response to the health emergency.

In a report dedicated to the ethics of research in emergency situations, WHO underlines that, while research involving significant risks for the individuals or populations involved always requires a request for a complete evaluation, for other types of research it is conceivable to adopt an “expedited” or “fast track” approach<sup>24</sup>.

In particular, “Protocols that involve a risk and a burden that is not more than minimal for the participants in the research can be reviewed on an expedited basis by one or more members (instead of the whole committee), if the EC has established written procedures that allow this procedure”.

The greater speed in the evaluation must not in any way lead to a “relaxation” of the ethical principles, but to guarantee the start of the research as timely as possible.

The EC evaluation activity must always consider the objectives of a research, the methods and the design of the study, an adequate evaluation of risks and benefits for the participants, the completeness and comprehensibility of the information to the patient and the involvement or otherwise of vulnerable subjects.

Other actions proposed by WHO to reduce the review time of emergency research projects include increasing the frequency of communications between EC components, by relying on online meetings, together with the preparation of standard protocol templates or parts of the study protocol that can be adapted by researchers in the drafting of their research protocol to be submitted to the EC. The preparation of the protocols should be carried out preventively, in anticipation of any future emergencies.

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<sup>23</sup> *Documento programmatico sulla ricerca osservazionale* del 3 settembre 2019 (versione 1.3) redatto da Centro di Ricerca Interateneo in Healthcare Research & Pharmacoepidemiology, Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI), Istituto Superiore di Sanità (ISS), Società Italiana di Farmacologia (SIF), Società Italiana di Medicina Farmaceutica (SIMeF).

<sup>24</sup> World Health Organization. *Research ethics in international epidemic response. Technical consultation WHO Technical Consultation. Geneva, Switzerland 10–11 June 2009. Meeting report*. Geneva: WHO; 2010.

### 3.3. EC procedures in emergency COVID-19: tips

As part of the COVID-19 emergency, the stringent measures for the containment of contagion require the EC to meet by online meeting. Here are some suggestions for the preparation and conduct of the EC sessions, particularly relevant in times of emergency:

- Appointment of one or more speakers among the members of the EC, dedicated to the detailed review of individual projects;
- Preparing checklists for documentation control;
- Preparation of checklists based on the indications of the STROBE Statement (STrengthening the Reporting of OBservational studies in Epidemiology) to facilitate the evaluation by the speakers and the sharing with other components (e.g., robustness of the study design, balance of risks-benefits, completeness and clarity of patient information documents, etc.)<sup>25</sup>;
- Establishing the maximum response times for the projects to be evaluated;
- Definition of pre-established time intervals for discussion of individual projects during the session, with variable intervals according to the risk level of the project;
- Timely recording of the meeting;
- Possibility of screen sharing and slide projection for researchers who want to present the study;
- Extraordinary electronic consultations for the approval of urgent projects, with a vote of abstention in case of non-response of the component;
- Possible use of digital signatures.

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<sup>25</sup> von Elm E, Altman DG, Egger M, et al. *STROBE Statement: linee guida per descrivere gli studi osservazionali. Traduzione italiana*. Terapia Evidence Based 2008;1:1:1-8.

## 4. Informed consent

Of all the observational research, in particular epidemiological, conducted in the context of the COVID-19 pandemic, only a part takes place within the healthcare facilities.

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

For some research, conducted not in the presence (e.g., online questionnaires, focus groups on electronic platforms), the use of an electronic consent may be admissible, provided that the consent itself is expressed by means of an “unequivocal positive act” in compliance with the legislation in force<sup>26</sup>.

The research that takes place in the health facilities can involve patients and health workers with different possibilities of interaction and expression of informed consent.

The reorganization of healthcare facilities put in place to deal with the pandemic emergency had substantial repercussions on the procedures for collecting informed consent for research purposes from patients with SARS-CoV-2 infection, as well as timescales and logistical difficulties due to containment of the contagion, have made it very difficult for healthcare professionals to comply with standard consent procedures.

The situation of the COVID-19 patient has some peculiarities that must be kept in mind, in order to prevent the acquisition of informed consent from becoming only a formal act and emptying its content and effectiveness.

This implies full knowledge and understanding of the information; therefore, it must be illustrated to the patient in an understandable way, compatibly with his clinical conditions. Informed consent cannot and must not be reduced to the affixing of a signature and the possible solutions to the problems related to it must not allow strategies that risk delegitimizing it.

In particular, the patient in isolation is in a situation of great vulnerability, firstly due to the lack of contact with his family or friends and, secondly, due to the safety conditions in which the health personnel must work, that is, with personal protective equipment devices that can make personal recognition difficult. It should also be considered that in the phases of greatest emergency of a pandemic, health workers can be so overwhelmed by events that they have difficulty or impossibility to relate to patients beyond strictly therapeutic interventions and often lifesaving treatments.

It is therefore necessary to outline procedures that, on the one hand, meet the needs of healthcare personnel and patients who face the emergency and, on the other, guarantee the ethical standards of research and patient protection.

The information 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 the rigor and empathy necessary for adequate communication and understanding.

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<sup>26</sup> Garante per la Protezione dei Dati Personalni. *Doveri - Come trattare correttamente i dati. Consenso.*

Although we refer here to observational studies, it can be useful to consider the indications for information to the patient and for the collection of informed consent proposed by the European Medicines Agency (EMA)<sup>27</sup> for clinical trials.

## 4.1. EMA guidance for informed consent in the COVID-19 emergency

- **Oral consent:** if the patient is in a condition that makes it difficult to obtain a written consent (e.g., if s/he is in isolation due to the infection in progress and it becomes necessary to reduce the risk for contamination) it is possible to provide oral consent in the presence of a witness, who can sign in place of the patient.
- **Deferred consent:** In the event that the patient is in critical condition that prevents obtaining consent directly (or through a legal representative) in time, it is possible to collect it at a later time, against a written declaration by the health personnel that formalizes the reasons.
- **Renewal of consent:** For research already in progress for which a renewal of consent is necessary (e.g., for subsequent changes to the protocol) the indications are to avoid having the patient go to the health facility for reconfirmation, and to apply alternative methods in forms that allow any subsequent checks, such as telephone or e-mail contact. In the case of the clinical trials, to which the EMA guidelines refer, the informed consents obtained through the aforementioned methods must be reconfirmed, through the standard procedures, as soon as possible.

## 4.2. Exemptions to consent

In the FAQ (Frequently Asked Question) published on the website of the Italian Data Protection Authority relating to data processing in the context of clinical trials and medical research in the context of the health emergency from COVID-19, it is indicated that, if for specific and proven reasons (e.g., impossibility of communication of information; disproportionate effort required by the procedure with the risk of making it impossible or prejudice the outcome of the research), it is not possible to acquire the interested party's informed consent even from third parties – as in the case of treatment of data referring to deceased or hospitalized patients in intensive care units – the owners who intend to carry out data treatments concerning **experimental studies and compassionate uses of medicines for human use**, for the treatment and prevention of the virus, in the emergency phase they are not obliged to submit the research project prior to evaluation of impact and prior consultation of the Data Protection Authority referred to in art. 110 of the Code regarding the protection of personal data<sup>28</sup>.

It is the opinion of the Working Group that, rather than a literal reading of the aforementioned document of the Data Protection Authority, a reading (which does not contemplate observational studies) which includes a wider variation of the notion of "experimental study", in line with the General Authorization n. 9/2016 – General authorization for the processing of personal data carried out for scientific research purposes – of 15 December 2016 (confirmed with provision of 13 December 2018, web document n. 9068972) is to be preferred. This Authorization, for the hypothesis of observational studies for which it is impossible to obtain the informed consent of the interested party, authorizes the processing of data if the

<sup>27</sup> European Medicines Agency. *Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. version 3, of 28/04/2020*. Brussels: European Commission; 2020. Disponibile all'indirizzo:

<sup>28</sup> Garante per la Protezione dei Dati Personalni. *FAQ - Trattamento dati nel contesto delle sperimentazioni cliniche e delle ricerche mediche nell'ambito dell'emergenza sanitaria da COVID-19*.

research project has obtained the favourable opinion of the competent territorial EC, expressly excluding the need for a prior assessment by the Data Protection Authority. In conclusion, it is reasonable to believe that, in the event of the impossibility of obtaining the consent of the interested parties, observational studies also take advantage of a derogation regime for the duration of the COVID-19 emergency. At the same time, as already expressed by the Working Group in another document<sup>29</sup>, to which we refer also for a more detailed argument, we express the hope of a clarification intervention by the same Data Protection Authority, in order to eliminate the residual margins of uncertainty, which can represent a significant obstacle for the most effective and profitable conducting scientific research activities.

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<sup>29</sup> Gruppo di Lavoro Bioetica COVID-19. *Protezione dei dati personali nell'emergenza COVID-19*. Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19 n. 42/2020). <https://www.iss.it/rapporti-covid-19>

## 5. Data sharing during the pandemic

To improve response to the pandemic event, national authorities and international organizations must strive to expand coordination between research groups, avoiding duplication of ongoing studies and promoting data aggregation and comparison of results between different institutes and research groups<sup>30,31</sup>.

The “data” of the research includes observations such as facts, images, measurements, recordings and files in various formats, which following particular analysis and interpretation processes give rise to “results”.

Research results and data must be readily available and accessible according to clear rules, interoperable with other data and available for reuse<sup>32</sup>.

To date, the debate within the scientific community has mainly concerned the sharing of clinical trial results, their registration and the provision of study datasets at the time of publication<sup>33</sup>.

However, following the spread of health emergencies since SARS in 2003, the need emerged for greater sharing of data deriving from studies not only interventional but also observational / epidemiological, from operational research, routine surveillance and monitoring of specific diseases<sup>34</sup>.

Accessibility and reuse of data are always necessary elements for the advancement of scientific knowledge, supported by the ethical requirement of the scientific and social value of the research activity<sup>35</sup>.

However, in a healthcare emergency context, the request for data sharing becomes even more stringent.

If, in fact, in an ordinary context, the idea that the researcher has the right to exclusive access to the data collected for his research projects is generally accepted<sup>36</sup>, in the health emergency, the professional interest of the individual researcher must necessarily be balanced with the wider interest of the community.

According to the WHO, the culture of sharing data and results should be the norm in health emergencies, and the decision not to share data and results should be substantiated by researchers and administrators at local, national and international level<sup>37</sup>.

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<sup>30</sup> Carra L, Cima S. *Liberate i dati per sconfiggere COVID*. *Scienza in rete*. 23/03/2020.

<sup>31</sup> Forastiere F, Micheli A, Salmaso S, Vineis P. *Epidemiologia e COVID-19 in Italia. Consentire e coordinare l'accesso ai dati per un'ampia collaborazione nelle valutazioni cliniche ed epidemiologiche*. *Epidemiol Prev* 2000;24(2):2020.

<sup>32</sup> Wilkinson M, Dumontier M, Aalbersberg I, et al. *The FAIR Guiding Principles for scientific data management and stewardship*. *Sci Data* 2016;3:160018.

<sup>33</sup> Ohmann C, Banzi R, Canham S, et al. *Sharing and reuse of individual participant data from clinical trials: principles and recommendations*. *BMJ Open* 2017;7:e018647.

<sup>34</sup> Langat P, Pisartchik D, Silva D, et al. *Is there a duty to share? Ethics of sharing research data in the context of public health emergencies*. *Public Health Ethics* 2011;4(1):4-11.

<sup>35</sup> Emanuel EJ, Wendler D, Grady C. *What makes clinical research ethical?* *JAMA* 2000;283(20):2701-11.

<sup>36</sup> Bernard C, Silva DS, Upshur R. *White paper on sample and data sharing during a pandemic: ethical challenges and considerations*. Toronto: University of Toronto Joint Centre for Bioethics; 2009.

<sup>37</sup> Modjarrad K, Moorthy VS, Millett P, Gsell PS, Roth C, Kieny MP. *Developing global norms for sharing data and results during public health emergencies*. *PLOS Medicine* 2016;13(1):e1001935.

Individuals and institutions are responsible for sharing the data for which consent is available or whose processing is necessary to safeguard the person's vital interests and to contain the effects of the pandemic, as also provided for by the regulation of the transfer of personal data to a third country or an international organization for important reasons of public interest, pursuant to art. 49 (and recital 112) of Regulation EU 2016/679, actively making them available, and not preventing others from doing so<sup>38</sup>.

In public health emergencies, the non-sharing of research data and results involves very high risks for individuals and communities at local, national and even global level.

The opportunity to share their data should entail some consequent responsibilities for the researcher:

- the researcher engaged in the production of information relating to a health emergency should also be predisposed to share preliminary results of his research, where the urgency and relevance of the information can reasonably balance the intrinsic limits of methodological robustness;
- the researcher is responsible for verifying and checking the accuracy of the results before disseminating them through peer review mechanisms internal to his own research group, pending an external review, and this is in case of complete results of one study and even more for the dissemination of preliminary data;
- if possible, the data should be collected in an interoperable way with other datasets, so as to allow their aggregation on a wider level.

When it is not possible to immediately publish the results in a peer reviewed journal, the researcher and the public or private institutions they belong to should disseminate the information through pre-publication mechanisms<sup>39</sup>.

Disclosure to the public of information relevant to public health emergencies should not affect subsequent publication in scientific journals<sup>40</sup>.

For their part, the editorial committees of the scientific journals should commit themselves to speeding up the review process of the submitted articles while maintaining the quality of the review itself and making available the accepted articles even before the official publication and possibly without a request for payment or at least at quota reduced. In this context, the role of the ECs also becomes crucial<sup>41</sup>.

In particular, the ECs can promote data sharing by asking to present together with the documentation for the evaluation of the studies a data sharing plan that establishes how the results and research data will be made available for the purpose of protecting public health and for others purposes, for the benefit of the population (countries) from which they come.

The ECs will have to distinguish between sharing research results through a timely and adequate publication and communication plan and effective sharing of pseudo-anonymized data sets.

Adequate incentives for researchers and reciprocity mechanisms are needed to promote data sharing.

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<sup>38</sup> Dye C, Bartolomeos K, Moorthy V, Kienyc MP. *Data sharing in public health emergencies: a call to researchers*. Bull World Health Organization 2016;94:158.

<sup>39</sup> Toronto International Data Release Workshop Authors. *Prepublication data sharing*. Nature 2009;461:168.

<sup>40</sup> International Committee of Medical Journal Editors. *Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals: overlapping publications*. ICMJE; 2016.

<sup>41</sup> Saxena A, Horby P, Amuasi J, et al. *Ethics preparedness: facilitating ethics review during outbreaks - recommendations from an expert panel*. BMC Med Ethics 2019;20:29.

Sharing data for the benefit of the community can entail a high cost for the researcher and must be adequately recognized by the institutions and researchers who make use of data made available for reuse.

The collection and analysis of data may require expert skills and important intellectual work, and the effort of those who design, collect and share their data must be recognized when publishing at the level of authorship and contributorship<sup>42</sup>.

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<sup>42</sup> Bierer BE, Crosas M, Pierce HH. [Data authorship as an incentive to data sharing](#). *N Engl J Med* 2017; 376:1684–7.

# Rapporti ISS COVID-19 in Italian

Available from <https://www.iss.it/rapporti-covid-19>

1. Gruppo di lavoro ISS Prevenzione e controllo delle Infezioni. *Indicazioni ad interim per l'effettuazione dell'isolamento e della assistenza sanitaria domiciliare nell'attuale contesto COVID-19.* Versione del 7 marzo 2020. Roma: Istituto Superiore di Sanità; 2020 (Rapporto ISS COVID-19, n. 1/2020)
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