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INFORMED CONSENT, CLINICAL TRIALS, COVID-19 AND HEALTH DATA

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Editorial

The impact of Covid-19 on informed consent

Laura Palazzani

The last 18 months have seen epochal changes in nearly all segments of our society. The Covid-19 pandemic has brought with itself so many changes also in our way of dealing with emergency in the context of medical and clinical settings.

Through a number of contributions that span the enormous impact that Covid-19 has had on the notion of informed consent, this special issue wants to highlight some of the changes that our society has already faced or will have to take into account in the near future when discussing informed consent, research, autonomy and ethics. Research for the preparation of this BioLaw Journal Special Issue has been conducted within the framework of the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective" (i-CONSENT), project funded by the European Union framework program H2020 (Grant Agreement n° 741856).

To begin with, by analysing the bioethical discussion and in particular the international and national documents with bioethical and biolegal relevance, I introduce the readers to the latest challenges posed to the notion of informed consent in clinical trials within the context of the Covid-19 pandemic, to be immediately followed and reinforced by Fabio Macioce's contribution, where he considers the specific vulnerabilities exposed by a pandemic. By underlining their medical, biological and socio-economical dimensions, Macioce pushes us to rethink the very idea of vulnerability -and its impact on the notion of informed consent for society more at large.

Carlo Petrini, Margherita Daverio and I are the authors involved with the part of this special issue concerned with Covid-19 and biomedical research. Petrini's contribution highlights how, to counter the Covid-19 pandemic, measures have been adopted to facilitate research, including observational research. Yet, some of these exceptional measures taken during the pandemic deserve particular attention as they could be also adopted in ordinary situations -helping us changing the paradigm when needed.

Daverio takes into account ethical and regulatory issues concerning vaccine research in the pandemic context, including a discussion of the controversial case of human challenge studies that have been on the news quite intensely during the first year of the pandemic. These studies need a careful ethical oversight in order to keep balanced risks and benefits for healthy volunteers enrolled in these trials, and the risk and benefits ratio assessment should clearly not result in a jeopardy of the informed consent process.

Lastly, my contribution, focused on clinical trials during Covid-19, provides a comprehensive overview of the main challenges for investigators-physicians and patient-participants, discussing their ethical implications for informed consent.

In the next section of the issue, Mirko Daniel Garasic takes issue with some of the more obscure implications of the widespread use of contact tracing apps during the Covid-19 pandemic. Starting off with an analysis of the increased use of this type of apps worldwide in the past year or so, Garasic questions the boundaries of the state of exception linked to some of those data collecting enterprise, pondering the relationship between public and private actors. Still on the path of technology and

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Editorial

pandemics, Alberto Tozzi and Giulia Cinelli discuss the role of artificial intelligence when applied to clinical trials in Covid-19 times, arguing that -among other things- given that Covid-19 has promoted the application of digital tools and of AI in clinical trials in order to limit personal contacts, this change might possibly speed up the adoption of AI solutions for clinical trials. This deserves a careful analysis of the potential ethical implications of such a revolution.

The subsequent theme considered is that of biological samples.

First, Monica Toraldo di Francia explains how biological samples, and the genetic personal data connected to them, are subject to special protection; focusing on this issue of great general bioethical importance, particularly in the current context of the Covid-19 pandemic, she highlights some theoretical-philosophical problems which underlie, from the very beginning, the bioethical and bio-juridical debate regarding both the status of biological samples donated for genetic research purposes, and the right of sample donors to choose whether or not to know individual results of potential clinical relevance.

Second, Pablo Enguer-Gosálbez, Jaime Fons-Martínez, Javier Díez-Domingo and colleagues bring to the issue some useful and timely data from the Spanish context, explaining how the Spanish biobanks have reacted to the Covid-19 pandemic, how they have managed the informed consent process during this exceptional time and what -possibly long-lasting- changes have been implemented during the emergency.

Finally, in the last section of the issue, we will engage with the shift of considerations related to the boundaries of health data – questioning how digital technologies (and the resulting rights and duties) might, should or will impact our sense of ownership of private data, hence the resulting need (or not) of our informed consent.

Andrea Parziale, Giovanni Comandé and Denise Amram's contribution maps out the ethical and legal implications of the controversial trend of "cutting corners" for data protection and informed consent in pre-marketing and post-marketing studies on medicines and medical devices in the context of the Covid-19 public health emergency.

In the last article, Federico De Montalvo Jääskeläinen deepens the analysis connected to health data, arguing -through the eyes of the EU Data Protection Regulation- that the pandemic should function as an opportunity to reconceptualize our ethical and legal understanding of personal medical data, privacy and, crucially connected to those, informed consent.

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Special issue

Informed consent for clinical research in the context of the Covid-19 pandemic between bioethics and biolaw: a general overview

Laura Palazzani*

ABSTRACT: The article examines the transformations of informed consent in the context of the Covid-19 pandemic, analysing the bioethical discussion and in particular the national and international documents relevant to bioethical and biolegal issues, in both institutional bodies and bioethics committees. Informed consent is analysed in the context of experimentation with treatments and vaccines, the use of biological samples and the processing of personal data.

KEYWORDS: Bioethics, biolaw, biological samples, data protection, informed consent

SUMMARY: 1. Research in emergency and pandemic conditions: bioethical and bio-juridical aspects – 2. Regulations for experimentation in emergency conditions: the reference regulatory framework – 3. Diversification of informed consent in research during the pandemic – 3.1. Informed consent and experimentation in the context of the pandemic – 3.2. Consent to the use of biological samples – 3.3. The right to privacy and protection of personal data and informed consent – 4. The "lessons learned" on informed consent in the context of the Covid-19 pandemic.

1. Research in emergency and pandemic conditions: bioethical and bio-juridical aspects

The Covid-19 pandemic has given a strong impetus to clinical research, with the aim of finding a treatment, prevention or cure in the shortest possible time to safeguard public health. These are "extraordinary" circumstances, characterized by uncertainty but also by a significant amount of pressure on research; this pressure has caused a climate of confusion and stress in both research workers and participants. In this context, a bioethical discussion and a bio-juridical reflection on informed consent has arisen, with particular reference to research in pandemic emergency conditions, with regard to treatments, cures and vaccines.

Even in the context of a non-emergency situation, informed consent to participate in research is not simple. The pressure of time can make it difficult to explain essential elements in clear and

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understandable language. Language barriers and inadequate cultural preparation can themselves cause difficulties in communication and comprehension[1].
Starting from the aspects already present in the regulatory and bioethical context, it is crucial to highlight the emerging elements of specificity relating to informed consent with reference to the Covid-19 pandemic.

2. Regulations for experimentation in emergency conditions: the reference regulatory framework

There are already more or less binding regulatory indications and international ethics on the topic of research in emergency conditions that also constitute the reference framework for reflection on informed consent in the context of the pandemic. These are regulations that generally emphasize the possibility of doing research on human subjects, even if they are unable to give informed consent or if urgent external conditions do not make it possible to request consent.
At the international level, the *Helsinki Declaration* of the World Medical Association (2013 latest revision) accepts documented written or oral consent in emergency conditions and in the presence of witnesses, in the absence of the usual consent conditions (art.26) and "delayed/postponed" consent, upon review of an ethics committee. The document provides a framing of the problem also with reference to "unproven treatments", in the absence of effective treatments, allowing participation with information on the possibility of it offering the hope of saving life, re-establishing health or alleviating suffering, with the "commitment of the researcher to give any information which may prove to be important during the research to the subject" (art.37).
Another source is the Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Guidelines 20 (2016), which explicitly refers to the pandemic[2], stressing the need, in such emergency conditions, to change standard procedures, while observing ethical principles. The document identifies a path, which may prove necessary, to accelerate the ethical review of research to facilitate relevant studies that can begin as soon as possible without compromising ethical requirements.
Even the *Universal Declaration of Bioethics and Human Rights* of UNESCO (2005), although it does not explicitly address the problem, indicates in art.8 - dedicated to respect for human vulnerability and personal integrity that in the application and advancement of scientific knowledge, medical practice and associated technologies, the vulnerability of the human person must be taken into account and provide for specific protection for individuals and groups in situations of particular difficulty, as well as respect for their personal integrity.

[1] As highlighted in L. PALAZZANI (edited by), *Special Issue on iConsent - Improving the Guidelines for Informed Consent, Including Vulnerable Populations, Under a Gender Perspective*, in *BioLaw Journal-Rivista di BioDiritto*, Special Issue 1/2019, pp. 154.
[2] CIOMS*, International Ethical Guidelines for Health-related Research Involving Humans* (2016), Guidelines 20: "Research in disasters and disease outbreaks. In fact, an acute disaster situation can require modifying standard procedures so that ethical principles can be upheld in the most expedient way possible. For example, while ethical oversight is essential in all research, accelerated ethical review during disasters may be necessary to ensure that valuable studies can begin as soon as possible without compromising ethical requirements".

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At the European level, it should be remembered that the *Additional Protocol Concerning Biomedical Research* (2005) at the Convention on Human Rights and Bioethics of the Bioethics Steering Committee of the Council of Europe justifies research in emergency conditions on humans if there is no alternative treatment of comparable effectiveness (art.5) and permits participation in research to the patient in emergency situations and not in a state to give their consent or who are able to consent when owing to the urgency there is no time to request informed consent or to obtain the authorisation of the legal representative. In such circumstances the following requirements are indispensable: the research cannot be carried out on persons in non-emergency conditions; there are no previously expressed objections; the research must be approved by an ethics committee; even when the research will not produce direct benefits, it could potentially contribute to the improvement of understanding capable of conferring benefit to the person concerned or to other persons who belong to the same category or those afflicted by the same disease or condition, entailing minimal risk and discomfort. Consent or authorization for continued participation shall be requested as soon as "reasonably possible".
Along the same lines are, the Integrated addendum to ICH E6 (R1), *Guideline for Good Clinical Practice,* (2016) and the World Health Organization, *Operational Guidelines for Ethics Committees that Review Biomedical Research* (Geneva, 2000).
Regulation 536/2014 of the European Parliament and the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20 / EC (2014), dedicates art. 35 to "Clinical Trials in Emergency Situations" and establishes the ethical conditions for research as: the presence of scientific grounds consistent with the potential given by participation in relation to a direct relevant benefit in terms of the improvement of health and well-being or in reducing suffering; absence of previously expressed objections to participation; the minimisation of risk and discomfort, compared to standard care and treatment[3]. However, consent must be given as soon as possible, i.e. when the subject regains the ability to provide it. It can be expressed in unwritten form with an impartial witness and the research approval of an ethics committee.

3. Diversification of informed consent in research during the pandemic

3.1. Informed consent and experimentation in the context of the pandemic

The World Medical Association points out that research is an "ethical imperative" when public health[4] is at stake: but research must always respect scientific standards of quality and validity. The danger, in

[3] "Scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition"; "the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject"; " the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition".
[4] WHO, *Ethical Standards for Research during Public Health Emergencies: Distilling Existing Guidance to Support COVID-19,* 2020, https://apps.who.int/iris/handle/10665/331507 (last accessed on June 1st, 2021); WHO, *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks*, 2016, https://apps.who.int/iris/handle/10665/250580 (last accessed on June 1st, 2021); Nuffield Council on Bioethics, *Research in Global Health*

times of pandemics, could be the efforts to push towards an acceleration of research, with the temptation to skip some of the "ordinary" phases of the trial process in the context of the "extraordinary" situation created by the pandemic[5]. The Covid-19 emergency has urged all researchers to start studies and trials[6], but it is important to monitor their quality so that the rights of research participants are protected, including the right to have adequate information and to have the opportunity to express free and informed consent.

Information to research participants must be clear from the moment of *recruitment*, explaining the criteria for inclusion and exclusion, with the balancing of the risks and benefits of participation or non-participation in the research, in the awareness that at times it may be or seem riskier not to participate than to participate, in the context of the pandemic where there are no validated therapies. Recruitment must protect the most vulnerable but not exclude them, because exclusion can however deprive them of new opportunities for treatment: the so-called particularly vulnerable categories, pregnant or breastfeeding women, children, people with disabilities, immigrants, should not be excluded a priori for "protective" purposes, without a reasonable scientific and ethical justification. Recruitment also includes "frontline workers" (physicians and nurses) who personally expose themselves to risks to help patients, not only in the area of treatment and care, but also in the context of research: the principle of solidarity can justify this priority, however, adequate information regarding the risks, and an equitable distribution between risks and benefits among the research participants must always be ensured, in order to avoid forms of conscious or unconscious exploitation. Participants should be treated with respect and selected in such a way that minimizes risks, maximizing the social value of the research.

Respect for *autonomy in participation* must always be central, ensuring the freedom and voluntariness in the participant's decision and avoiding their feeling pressured to take part or even feeling guilty for not participating towards others and society in general. The context of the pandemic risks spreading the idea that every attempt must always be made, no matter what, however, we cannot expose people to unnecessary risks, with the sole aim of acquiring new knowledge. Some groups are particularly susceptible to these dynamics: for example, in China, the first large block of patients will be the military. Even in Western contexts, the military are vulnerable due to the possible reduction of autonomy owing to obligations towards those in a superior hierarchical position. Exposing participants to unnecessary risks is ethically unacceptable. Participation in research in the absence of alternatives makes the choice a particularly delicate one; it is imperative to avoid misunderstandings with the participant about the role of research, which means, clarifying the experimental nature and uncertainty of the research and proposing possible alternative paths, without resorting to forms of "experimental persistence". In the context of a severe and even fatal pandemic infection, many people may be willing to take a high risk or use unproven agents in a clinical trial or outside the framework of

Emergencies: Ethical Issues, 2020, https://www.nuffieldbioethics.org/publications/research-in-global-health-emergencies (last accessed on June 1st, 2021).

[5] In this perspective, administrative processes for reviewing research protocols must be accelerated and simplified if these protocols are related to the treatment, prevention or diagnosis of infections caused by SARS-CoV-2.

[6] CIOMS, *International Ethical Guidelines for Health-related Research Involving Humans*, Guidelines 1: Without scientific validity, the research lacks social value and must not be conducted (see Guideline 1 – Scientific and Social value and respect for rights).

a clinical trial. It is essential that researchers realistically balance potential benefits and risks and communicate them in a clear and transparent manner to potential participants. If participation in the study, in pandemic times, increases the risks for participants, this should be carefully taken into consideration, remembering that safety is a priority. The justification for *compassionate studies* must always provide an opening to the possible benefits for the patient: a study that has as its objective only the indirect benefits for society is to be considered unethical. It is also important to discourage patients from participating in studies outside clinical settings: on-line experimentation or self-experimentation involves dangers in the absence of medical supervision and monitoring.

Even if research is carried out under difficult and emergency conditions, informed consent must still be collected to the extent possible in order to ensure that those who decide to participate in the research have actually understood and evaluated the risks and benefits and are able to make a conscious and informed decision. *Informed consent remains a fundamental requirement***;** the understanding of the risks and benefits by the participant must be ascertained, avoiding, in the context of the pandemic, the perception of risks being reduced in the face of expectations that are not always reasonable[7]. Oral or photographed/video recorded consent in the presence of witnesses (selected according to impartial criteria justified by the investigator) is also acceptable; digital technologies for informed consent must be implemented (avoiding paper and improving and speeding up information for patients). When it is not possible to obtain informed consent in the usual way, due to movement restrictions or isolation of patients, alternative procedures should be considered, but as soon as the situation permits, informed consent must still be obtained. Researchers must consider the particular condition of vulnerability in the context of the pandemic, the pressure of time of the research may not coincide with the time for maturing consent: despite the external pressure, the uncertainties of the participant's decision must be respected, considering that fear, discomfort, stress can compromise the understanding of the information and the decision to participate itself. In the event of changes to protocols, which are frequent due to the evolution of the pandemic, consent must, to the extent possible, be requested again with the appropriate changes.

The World Health Organization in the document *Ethical Standards for Research during Public Health Emergencies: Distilling Existing Guidance to Support COVID-19*[8] emphasizes that informed consent, as a fundamental requirement of research even in pandemic emergency conditions, also requires an increase in responsibility on the part of researchers and ethics committees in ensuring that research activities do not proceed without a reasonable scientific basis aimed at safety and efficacy, and that risks are minimized "to the extent possible" ("to the extent reasonably possible"). An emphasized element is the *problematicity in confusing the dual role of physician and researcher***:** it is desirable for the researcher and the treating physician not to be the same person, since this dual role could exert an indirect pressure to participate on the patient, who, may fear that non-participation could lead to a loss or at least a reduction in care and attention. Furthermore, researchers and sponsors should

[7] COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Statement on Human Rights Considerations Relevant to the COVID-19 Pandemic*, 14 April 2020, https://rm.coe.int/inf-2020-2-statement-covid19-e/16809e2785 (last accessed on May 31st, 2021).

[8] COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Statement on Human Rights Considerations Relevant to the COVID-19 Pandemic*, cit.

ensure that individuals participating in the research can access the *possible benefits resulting from their participation*. If research results are proven safe and effective, such results should be made available to participants as soon as possible, including when possible access to drugs or interventions not yet registered, and nevertheless making, every effort to provide equitable access to the benefits of the research conducted under emergency conditions. These elements should also be included in the informed consent.

The European Medicines Agency (EMA) has also expressed its stand on the subject, together with Heads of Medicines Agencies (HMA) in the document *Guidance on the Management of Clinical Trials During the Covid-19 Pandemic* (28 April 2020) in which it is emphasized that *the sponsors* should be aware of the pressure on doctors to carefully evaluate the relevance and appropriateness of enrollment in clinical trials and that patients should be informed *of alternatives to written informed consent* (e.g. oral consent, in the presence of a witness, deferred consent, renewal of consent or reconfirmation for changes to the protocol by telephone or e-mail, to avoid participants being exposed to unnecessary risks). The informed consent obtained through these methods must be reconfirmed, through standard procedures, as soon as possible and the reasons for the impossibility of obtaining customary informed consent from the patient must be appropriately motivated and recorded by the researcher.

The European Commission has issued specific guidelines *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic* (2020) aimed at ensuring the conducting of *clinical trials* during the Covid-19 epidemic, given the numerous difficulties, including the restriction on visits to healthcare facilities, the scarce availability of resources all concentrated in dealing with the emergency, the need for isolation and quarantine for some participants in the studies[9]. On informed consent, it reiterates that the opportunity to obtain consent from subjects must always be given priority over other solutions, even in cases of subjects who are in isolation, for which cameras or photographs of the documentation can be used taken through the transparent isolation barriers. In the case of temporary consent in verbal form, the presence of an impartial witness is required to certify that the consent has been given and signed and dated on the informed consent document. It is up to the investigator to certify the method of selection of the impartial witness[10].

The Bioethics Committee of the Council of Europe (DH-BIO) in the document *Statement in the Context of the COVID19 Crisis* (2020) underlines how the case of "compulsory isolation" for a seriously infectious disease, such as a pandemic, falls within the exceptions to informed consent for public health protection reasons. This exception is provided for in art. 8 of the *Convention on Human Rights and Bioethics* (1997) which concerns emergency situations, which include the pandemic. The document states that in these conditions, when the appropriate consent cannot be obtained, any medical intervention that proves to be of direct benefit to the individual is possible. As part of the research, DH-BIO reiterates the requirement of respect for human rights reflected in the Oviedo

[9] European Medicines Agency (EMA), *Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic*, available https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf (last accessed on May 31st, 2021).

[10] In Italy, the Italian Medicines Agency (AIFA) has explained these guidelines on informed consent in the Communication of 12 March 2020, updated on 7 April 2020.

Convention, which does not provide for exceptions in art.16 and 17 to the protection provided for research participants (permitting as the only conditions, when there is no comparable alternative in terms of effectiveness to research on human beings, the non-disproportion of the risks compared to the potential benefits, in addition to the approval of the ethics committee). The Committee of the Council of Europe underlines how the Additional Protocol on biomedical research usefully completes the Convention in art.19 in the context of the conditions for research in emergency conditions. If the person is not in a state to give consent due to a lack of awareness and/or the urgency of the situation, consent can be given by the legal representative, with the approval of the committee and verification of the absence of explicit objection by the subject.

In the *Position of the European Network of Research Ethics Committees (EUREC) on the Responsibility of Research Ethics Committees During the COVID-19 Pandemic* (2020)[11] it is emphasized that informed consent must remain compliant with European and national regulations. It recognizes that national regulations may differ in Europe. The proposed simplification of consents in the context of the pandemic should be taken into consideration by the European ethics committees, as part of the primary objective of protecting the dignity, rights and safety of participants, patients and healthy volunteers, in the context of medical studies. The document stresses that "the pressure exerted on medical research must not lead to the research or experimentation of drugs on humans without compliance with the ethical standards applicable to medical research".

In the context of *vaccine research*, some specific aspects emerge, with regard to experimentation. The World Medical Association in the document *Key Criteria for the Ethical Acceptability of COVID-19 Human Challenge Studies* (2020) returns to the topic (after the document *Human Challenge Trials for Vaccine Development: Regulatory Considerations*, 2016) addressing the specific issue of vaccine testing through studies with intentional controlled infection of healthy volunteers, with a dose high enough to cause disease and thereby stimulate the immune system, but not so high as to cause disease in a severe form. These are studies that could be justified in principle given the urgency of research on vaccines, the need to accelerate research due to the speed of the spread of the virus, and its global expansion. There is a broad bioethical discussion on the issue with particular reference to the proportionality or disproportionality in balancing benefits and risks. The potential benefits of this research are: the possibility of speeding up research times; the reduction in the number of volunteers compared to the usual clinical trials that involve tens of thousands of participants, compared to numbers always lower than one hundred for *Human Challenge Trials*; the increase in information obtainable in less time; cost reduction. But certainly the risks are high since there is no cure and no proof of efficacy of the treatments available, therefore even with the risk of death for participants. The basic principle of clinical ethics should be remembered which allows experimentation on condition that there is a minimizing of the risks for subjects and maximizing of the benefits: by their nature, the *Human Challenges Trials* would seem to contradict this fundamental precept. The World Medical Association underlines certain ethical requirements, while opening to this possibility albeit in a limited way under certain conditions, including also informed consent, which must be particularly rigorous

[11] *Position of the European Network of Research Ethics Committees (EUREC) on the Responsibility of Research Ethics Committees During the COVID-19 Pandemic*, 2020, http://www.eurecnet.org/documents/EUREC_Positionpaper_March_2021.pdf (last accessed on May 31st, 2021).

due to the potentially high risk and uncertainty, the complexity of the information that must be properly understood. Consent must be reviewed during the study when new relevant risk data are available after the study has begun. The selection of participants at the time of enrollment must include full understanding of the potential risks and voluntariness: in this sense, those who come from difficult social backgrounds must be excluded precisely because of the risk of an inadequate understanding and the possibility of their exploitation for scientific advantage. The document insists on the need for scientific justification for the research, which must be able to produce relevant results for public health and which cannot be obtained in another less risky manner, on the importance of a preliminary systematic risk assessment (quantification of risks, comparison with other studies, clarification strategies to minimize risks) and on the relevance of transparent public involvement of research participants, the guarantee of long-term monitoring, the international coordination of research, the ethical review of experts. In addition, it also insists on comprehension tests, which make it possible to verify the acquisition of full awareness regarding the choice. The ethical reservations about these studies concern, in the light of the bioethical principle of the primacy of human dignity over the interest of science (shared by international bioethics and bio-law), the acceptability of the sacrifice involved in the exposure to risks for the community by subordinating personal good to public good, the duty of the researcher to intervene on subjects only in a proportionate way as well as the problematic nature of reimbursements or even compensation that call into question the bioethical principle of free participation and the prohibition of the sale or purchase of the body (exposing poor people to disproportionate risks purely for economic objectives).

3.2. Consent to the use of biological samples

In the context of the pandemic, specific issues arise in relation to informed consent for biological samples.

It should be specified to the subject whether the samples, taken using different methods, *are for diagnostic purposes only or also for research purposes.* The possibility of tests for the diagnosis of the presence or absence of the infection is an opportunity for individuals and for the community, but it must not hide research paths. The purposes of the test must be clarified in the consent, specifying whether it is an epidemiological study, a health surveillance on specific populations for public health purposes, a screening test, a diagnostic test and/or biobanking. The possibility of biobanking must be made explicit in the consent, with clarifications - as for any research - on the time and purpose of the research, on the possible destruction or preservation of the samples for future use, making it clear that it is directly or indirectly related to Covid-19 research. The storage location of the biobank and any transfer abroad of the biological material should also be specified, including specification of adequate privacy guarantees[12]. What is collected, where it is collected, how it is collected, for what purposes, and for how long must be made clear. It should also be specified whether the samples will be pseudo-anonymized (in accordance with current legislation) and in the case of interruption of the research (by

[12] ISTITUTO SUPERIORE DI SANITÀ, ISS COVID-19, *Translational Research Working Group 2020, Recommendations for collection, transport and storage of COVID-19 biological samples*. Version of April 15, 2020., pp. 19, https://www.iss.it/documents/20126/0/Rapporto+ISS+COVID-19+n.+13+campioni+EN.pdf/19533b9b-a811-ce0e-a631-e64b040bca77?t=1589362071454 (last accessed on June 1st, 2021).

the researcher or the participant) whether these will be destroyed or anonymized. Researchers should make information public as soon as it becomes available. It should be specified whether genetic analyzes will be carried out as well as any possible strategies in the event of "unexpected results", i.e. results not expected but of clinical relevance for prevention, diagnosis or treatments.

A specific question emerges in relation to *mandatory or voluntary testing*: mandatoriness can be diversified to *varying degrees and forms*; voluntariness can indicate *different situations* (e.g. it is one thing if the test is proposed by the health facility to its employees, and another thing if it is requested by the person concerned for his/her own purposes). It must be specified in the consent if the request for the test comes from the interested party or if it comes from institutions for health surveillance and/or public health purposes. It is necessary to ensure the availability of material - i.e. serological test kits and swab reagents - for tests required for public health purposes (such as those carried out on healthcare professionals) and for urgent clinical purposes.

The Word Health Organization in the document *Ethical Standards for Research During Public Health Emergencies: Distilling Existing Guidance to Support COVID-19* stresses that researchers should inform potential participants about the circumstances in which biological samples may be shared. In the context of the pandemic the sharing of biological samples becomes a possibility which participants and stakeholders must be informed of. To the extent that samples have the potential to generate responses that are useful to public health, there is an ethical obligation to share the information. Given the urgency of the research, consent can be broad and dynamic, open to future research uses of the samples. The sharing of biological samples can/should be a viable option[13] alongside the option of biological sample control (restricted consent). Sharing takes on a humanitarian and supportive value for the future of research, in helping to reduce the suffering of present and future patients. It is the responsibility of the researcher and the ethics committee to verify that the consents are understandable and avoid the risks of harm and exploitation of those who already suffer disadvantages and hardships. The ethical conditions for sharing samples must be equitable and responsible: equitable, means allowing equal access to benefits; responsible, means ensuring that sharing is effective and safe. In this sense, public information on the importance of research on biological samples would be desirable. In the event of a denial, the samples must be anonymized and destroyed once the purpose for which they were collected in the emergency has been finalized. Similarly, samples must be anonymized in the event of the patient's death, in the absence of his/her explicit consent to Covid-19 biobanking.

At the European level as at the national level, there is no regulation specifically dedicated to research biobanking, but research on biological samples is regulated in a contextual manner to the regulation on data processing for scientific purposes[14].

[13] COMITÉ DE BIOÉTICA DE ESPANA*, Informe sobre los requisitos ético-legales en la investigatcion con datos de salud y muestras biologicas en el marco de la pandemia de Covid-19*, April 2020, http://assets.comitedebioetica.es/files/documentacion/Informe%20CBE%20investigacion%20COVID-19.pdf (last accessed on June 1st, 2021).

[14] To represent the ethical-regulatory set-up of informed consent to research biobanking, also using the tool of analogy, both legislative acts with binding legal value (European Regulation, Directive; Legislative Decree, Provision, Authorization, etc.) and documents (Recommendation, Convention, Declaration, etc.) are proposed in order to direct, recommending good practices but these are not binding.

The Convention on Human Rights and Bioethics (Oviedo 1997) of the Council of Europe explicitly states: "when a part of the human body is removed in the event of an intervention, it cannot be preserved and used for purposes other than those for which it was collected and in accordance with appropriate information and consent procedures". The *Recommendation 2006/4* of the Council of Europe, replaced and updated, by the *Recommendation 2016/6 on Research on Biological Materials of Human Origin* specifies the defense of physical integrity and privacy; the right of every individual to accept or refuse to contribute to research; transparency of governance; the minimization of the physical risk of the withdrawal and risk to private life (for the individual and the family) and the proportion with respect to the benefits obtainable from the research (risks per group of individuals); the refusal to give consent or the withdrawal of consent to collection and use for research must not lead to any discrimination (in particular in the context of the right to treatment); the gratuity of the donation; the anonymization and use of identifiable samples must be justified in the research and evaluated by an ethics committee; the spread of research knowledge; the traceability of biological materials. The recommendation states that biological materials can be removed from the body of a deceased person to be kept for future research only with the consent or authorization required by law, preceded by adequate information, including on the right to refuse. Additionally, biological materials should not be removed to be stored for future research if the deceased person is known to have objected to their post-mortem preservation.

In the context of the Italian regulation on post-mortem research biobanking, reference can be made to Law 10 February 2020, n. 10 *Rules on the disposition of one's body and post-mortem tissues for study, training and scientific research purposes*. The modalities and requirements of consent to the post-mortem donation of one's own body and parts of the body (biological samples) are established by article 3: the declaration of consent must be drawn up, in analogy with the Law 219/2017 on informed consent and on advance treatment directives, in the forms provided for by the directives for advance treatment, that is to say by public act, by authenticated private act, or by private act delivered personally by the subscriber to the civil status office of the municipality of residence. Furthermore, the declaration of consent must be delivered to the Local Health Authority to which he/she belongs, which is responsible for keeping it and electronically transmitting it to the Advance Treatment Directive Database. Withdrawal of consent can be done at any time in the same way. Unlike Law 219/2017, the declaration of consent for post-mortem donation requires a trustee to be appointed who is responsible for communicating the existence of the consent to the doctor ascertaining the death.

3.3. The right to privacy and protection of personal data and informed consent

The collection of data as part of participation in research in the context of the pandemic must be fast and accurate, according to the criteria of *quality, accessibility, transparency, standardization, interoperability. Data protection* must be guaranteed, but it must not prevent measures against the pandemic, since the fight against the pandemic is a value shared by all nations, in the interest of all humanity.

The (EU) Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016, *General Data Protection Regulation*, allows, in exceptional circumstances such as an epidemic and for reasons of public interest, temporarily to process data having the public interest as a legitimate legal basis of

the processing, even in the absence of consent. This does not relieve the data controllers and processors from protection of the personal data of the persons involved, but the emergency is recognized as a "legal condition that can legitimize restrictions on freedoms by providing for proportionate and limited restrictions in time" and even exemptions to privacy. The necessity, proportionality, appropriateness of such exceptions, in the context of a democratic society, must comply with the Charter of Fundamental Rights of the European Union (2000) and the *European Convention for the Protection of Human Rights and Fundamental Freedoms* (1958) subject to the control of European Court of Justice and the European Court of Human Rights. Each measure must be properly documented.

The European Data Protection Board (EDPB) in the document Statement by the EDPB Chair on the Processing of Personal Data in the Context of the Covid-19 Outbreak, adopted on March 16, 2020, clarifies that these restrictions must be proportionate and confined to the period of emergency, and that in any case, the data controllers and processors must ensure the protection of the personal data of the data subjects. In particular, the Committee affirms that the personal data necessary to achieve the objectives pursued should be processed *for specific and explicit purposes,* the data subjects should receive *transparent information* on the processing activities carried out and their main characteristics, including the retention period of the collected data, the information should be easily accessible and formulated in simple and clear language, the measures put in place to manage the current emergency and the related decision-making process must be adequate and documented.

The Joint Statement on the Right to Data Protection in the Context of the COVID-19 Pandemic (by Alessandra Pierucci, Chair of the Committee of Convention 108 and Jean-Philippe Walter, Data Protection Commissioner of the Council of Europe Strasbourg, 30 March 2020), underlines that the guiding ethical principle must remain the primacy of the human being and the adoption of professional standards in the use of health data in the guarantee of fundamental rights and freedoms, with particular reference to the right to privacy. The sharing of data in the context of health professionals must be allowed; in the context of public communication by the authorities, data on the health of specific individuals should be avoided[15].

The DH-BIO Bioethics Committee at the Council of Europe in the *Statement in the Context of the COVID19 Crisis* (2020) recalls art. 10 of the *Oviedo Convention* concerning the right to privacy of information in the field of health, reaffirming the principle introduced in art. 8 of the *European Convention for the Protection of Human Rights and Fundamental Freedoms.* The possibility of this restriction on the exercise of rights including the right to privacy is explicit in art. 26. These exceptions are aimed at collective protection and safeguarding public health. But such restrictions must be

[15] *Joint Statement on the right to data protection in the context of the COVID-19 pandemic by Alessandra Pierucci, Chair of the Committee of Convention 108 and Jean-Philippe Walter, Data Protection Commissioner of the Council of Europe*, 30 March 2020, https://www.coe.int/en/web/data-protection/statement-by-alessandra-pierucci-and-jean-philippe-walter (last accessed on June 1st, 2021); EUROPEAN DATA PROTECTION BOARD, *Statement on the Processing of Personal Data in the Context of the COVID-19 Outbreak*, 19 March 2020, https://edpb.europa.eu/news/news/2020/statement-processing-personal-data-context-covid-19-outbreak_en (last accessed on June 1st, 2021). See also RESEARCH DATA ALLIANCE (RDA), *COVID-19 Working Group, Recommendations and Guidelines*, 15 May 2020, https://www.rd-alliance.org/15-may-2020-fourth-release-rda-covid-19-guidelines-and-recommendations (last accessed on May 31st, 2021).

prescribed by law in democratic societies and must be interpreted within the framework of the criteria defined by the European Court of Human Rights, in particular necessity and proportionality.

In Italy the Law Decree n. 14 of 9 March 2020, *Provisions for the strengthening of the National Health Service in relation to the COVID-19* emergency clarifies how the processing of data collected during the emergency period must take place in compliance with the principles set out in art.5 of the European Regulation 679/2016 adopting proportional measures with regard to necessity. Art. 14 of the decree law provides, until the end of the state of emergency, the possibility of simplifying some aspects of the processing of personal data for reasons of public interest in the public health sector, mentioning the diagnosis and health care of those infected, but it could also be extended to research. Paragraph 5 of the same article introduces the possibility of omitting the information or providing simplified information, after verbal communication of the limitation. Paragraph 4 allows the data controller or data processor to assign, under their own responsibility, specific tasks and functions related to the processing of personal data to individuals, expressly designated, who operate under their authority, in a simplified manner, including verbally. A report on the *Protection of personal data in the COVID-19 emergency* was prepared on the subject by the Covid-19 Bioethics Working Group no. 42 2020 (May 28, 2020).

As part of the "exemptions to consent" in a FAQ (Frequently Asked Question) published on the website of the Guarantor for the Protection of Personal Data relating to the *Processing of data in the context of clinical trials and medical research in the context of the COVID-19 health emergency*, 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 informed consent of the interested party 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.

In compliance with the regulation on privacy (through pseudo-anonymization), in pandemic times consideration must be given to the importance of *sharing data* in the scientific community for an efficient impact of results, considering also the risks and potential damage of not sharing data: data are a precious asset and an individual contribution to the advancement of knowledge with also a potential direct benefit, in addition to the indirect benefit for society. It is essential to monitor the correct storage of data in reliable and certified public deposits, with the guarantees of compliance with regulations and ethical requirements, preventing abuses[16]. According to the World Health

[16] UNESCO International Bioethics Committee (IBC), World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), *Statement on Covid-19: Ethical Considerations from a Global Perspective* (April 2020): "there is a need for coordination of international efforts and the formulation of a common understanding of ethical review processes; An oversight committee for responsible research during this pandemic on a global level needs to be urgently created". The Statement is https://en.unesco.org/themes/ethics-science-and-technology/comest (last accessed on May 31st, 2021).

Organization, 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 justified by researchers and administrators at local, national and international levels.

4. The "lessons learned" on informed consent in the context of the Covid-19 pandemic

Informed consent plays an increasingly important role in allowing the patient to make an *autonomous choice,* based on full awareness and responsibility in the context of the Covid-19 pandemic. The patient must also be aware of the particular conditions of vulnerability, with an equitable and proportionate distribution of risks and benefits in order to minimize the risks, maximizing the social value of the research. The researcher's understanding of the risks must be ascertained (possibly not coinciding with that of the treating physician), avoiding, in the context of the pandemic, the perception of risks being decreased in the face of expectations that are not always reasonable and realistic. Despite external pressure, the importance of respecting the uncertainties of the participant's decision and the decision-making process emerges, considering that fear and discomfort can compromise serene patient participation. The pandemic has also prompted the spread of alternative methods to written consent (oral or photographed/video recorded consent in the presence of witnesses) as well as the implementation of the use of digital technologies speed up and improve information for patients.
In the field of biological samples, the importance of the specification of the purpose of the research is becoming increasingly evident, and the strong driving force of solidarity in the sharing of biological samples as a possible option, as opposed to the trend towards individualism. Sharing takes on a humanitarian and supportive value, as part of so-called participatory development, in the context of biomedical research given the urgency of responses for the community. Data collection in the context of participation in pandemic research must be fast and accurate, according to the criteria of quality, accessibility, transparency, standardization, interoperability. Data protection must be guaranteed, but it must not hinder measures against the pandemic, since the fight against the pandemic is a value shared by all nations, as a global interest of all humanity. There are many documents that allow "exceptions" to consent: what emerges is the importance of sharing data in the scientific community in order to achieve an efficient impact of the results for the "global common good".

Informed consent and group vulnerability in the context of the pandemic

Fabio Macioce*

ABSTRACT: Group vulnerability is a standard issue in bioethics. Research ethics guidelines highlight the need for protection of vulnerable participants, and clinical trials are ruled by ethical and legal principles that concern possible health inequities experienced by vulnerable populations. In both the literature and the regulation, two conceptions of vulnerability are at work. On the one hand, the inherent vulnerability that is part of the human condition; on the other hand, the *situational* vulnerability that is associated with specific contextual factors, and that point out either a reduced autonomy or a greater risk of harms for individuals belonging to some groups. Both these two conceptions of vulnerability are exacerbated during a pandemic; on the one hand, specific populations are at heightened risk for medical complications from the virus (elderly, or immunodepressed); on the other hand, specific groups experience an increased vulnerability due to the social determinants of health, which influence individual resilience and exacerbate the impact of the virus. Among the many (income distribution, education and literacy, working condition, house and living conditions, disability, access to health services, etc.) the dramatic reduction of the space for free and informed consent, because of the mental and physical adverse effects coming from social isolation, age, culture, literacy, is relevant for both clinical research and practice. In this paper, I will discuss challenges for the informed consent in the context of the Covid-19 pandemic, with specific consideration of the condition of vulnerable groups.

KEYWORDS: Covid-19; informed consent; research ethics; vulnerability

SUMMARY: 1. Introduction – 2. Vulnerability as a bioethical concept – 3. Group vulnerability and the pandemic – 4. Trials and informed consent: the case of vulnerable groups – 5. Conclusions.

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1. Introduction

As witnessed during the 2009 H1N1 pandemic and the 2003 SARS epidemic, in the context of a pandemic a great amount of attention is paid - by health authorities, media, policy makers, etc. - to the protection of those members of the population who are exposed to a higher risk from a clinical point of view, or in relation to complications resulting from infections caused by viruses or bacteria. However, it is important to recognize that significant conditions of vulnerability can depend on social factors (referred to as social determinants of health), which influence people's resilience and can exacerbate the impacts of the pandemic[1]. For this reason, it is crucial to identify the factors that can produce, or aggravate, the vulnerability of certain groups of people in the context of a pandemic, because only in this way is it possible to prepare adequate forms of protection and guide the procedures and practices of research in order to guarantee the dignity and rights of people in conditions of vulnerability, also with reference to the processes of information and expression of consent.

In this article, I discuss the category of group vulnerability, and the consequences related to the processes of obtaining informed consent, with specific reference to the context of the pandemic. After a brief *explicatio terminorum* relating to the use, within the field of bioethics, of the category of group vulnerability and its usefulness, I discuss the repercussions of the pandemic on this category, and how the pandemic has consequently altered the traditional "map" of vulnerable groups. Finally, in the third part, I discuss the ways in which the processes of obtaining consent can represent an effective tool for mitigating the vulnerability - of people and groups - even in the context of a pandemic.

2. Vulnerability as a bioethical concept

Recourse to the notion of vulnerable groups, in literature and in regulation in the field of bioethics, is as old and widespread as it is characterized by its wide margins of vagueness; if on the one hand this vagueness is understandable, and linked to the multiplicity and unpredictability of the conditions which represent a particular exposure to risk and a reduced ability to cope with it, on the other hand it does not contribute to ensuring the objective of clarity and precision which, as stated, is particularly useful in the context of a pandemic. In fact, not only is the notion of vulnerable groups widely used in texts with normative value and in other types of documents (guidelines, opinions, recommendations) but it has entered the common lexicon of bioethics[2] especially in relation to the profile of consent, and with reference above all to the field of biomedical research. And yet, at the

[1] J.P. GAROON, P.S. DUGGAN, *Discourses of disease, discourses of disadvantage: A critical analysis of National Pandemic Influenza Preparedness Plans*, in *Social Science and Medicine*, 67(7), 2008, 1133-1142; INTERNATIONAL CENTRE FOR INFECTIOUS DISEASES, *Issues in Pandemic Influenza Responses for Marginalized Urban Populations: Key Findings and Recommendations from Consultation Meetings and Key Informant Interviews*, 2010 http://www.icid.com/files/Marg_Pop_Influenza/Issues_in_Pandemic_Influenza_Responses_for_Marginalized_Ubran_Populations_English_FINAL.pdf (last visited 02/06/2021)

[2] H. TEN HAVE, *Respect for Human Vulnerability: The Emergence of a New Principle in Bioethics*, in *Bioethical Inquiry*, 12, 2015, p. 396; M. THOMSON, *Bioethics & vulnerability: Recasting the objects of ethical concern*. In *Emory Law Journal*, 67(6), 2018, p. 1218.

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same time, without a clear understanding of what exactly vulnerable groups are, and the factors which determine this vulnerability, can constitute a very serious obstacle for the provision of adequate forms of protection precisely in the context of clinical trials and the procedures for obtaining informed consent.

Now, the objective of protecting subjects and categories of subjects considered to be particularly fragile, or in need of specific forms of protection, has been perceived since the dawn of bioethics, that is, since the Nuremberg Code and the Declaration of Helsinki[3]. This initial imprint, will, in some way, also remain in subsequent documents: the need to grant special protection to vulnerable subjects, and to groups or categories of subjects considered to be particularly fragile, or exposed to particular risks, will be continually reaffirmed in all the documents related to research in the biomedical field, while, on the one hand, however, being based on a lack of definitional clarity, as a result of which, on the other hand, the identification of vulnerable subjects will continue to be inaccurate, and to some extent taken for granted[4]. In this sense, vulnerability in bioethics has tended to have the meaning of drawing attention to exposure to a *heightened* risk of harm, and/or to an ability to defend oneself or cope with this risk that is *lower* than standard; this is due to particularly complex circumstances, or to reduced subjective capacities, or to specific situations involving a reduced ability to protect oneself. So, certainly intuitively, and with a great deal of common sense, we can qualify minors, or people with psychiatric disorders, or patients in intensive care, as examples of vulnerable subjects/categories. Equally, however, an intuitive or common sense classification can not suffice, if the imposition of specific obligations for special protection, or additional guarantees[5] ensue.

A first explicit reference to vulnerability, and more specifically to group vulnerability, can be found in the Belmont Report[6], in which vulnerability is considered under three profiles: in relation to the issue of incentives, because "inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable"; with reference to the risk/benefit balance of research, since in the case of research including "vulnerable populations" this involvement must itself be demonstrated as necessary; finally, as a matter of justice, to prevent socio-economically weaker groups from being manipulated, exploited, and unduly involved in research. In the latter case, a first type of vulnerable group is also outlined: "Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or

[3] W. Rogers, C. Mackenzie, S. Dodds, *Why bioethics needs a concept of vulnerability*, in *International Journal of Feminist Approaches to Bioethics*, Vol. 5, No. 2, 2012, p. 14.

[4] W. Rogers, *Vulnerability and bioethics*, in C. Mackenzie, W. Rogers, S. Dodds (Eds.), *Vulnerability: new essays in ethics and feminist philosophy*, New York, 2014, p. 62.

[5] S.A. Hurst, *Vulnerability in research and health care; describing the elephant in the room?*, in *Bioethics*, 22(4), 2008, pp. 191-202.

[6] National Commission for the Protection of Human Subjects of Biomedical and Behavior Research, *The Belmont Report*, 1979 https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html (last visited 02/06/2021)

because they are easy to manipulate as a result of their illness or socioeconomic condition".[7] The Belmont Report approach, however, is indicative of a trend that seems to characterize all subsequent legislative and regulatory provisions, leaving unresolved the ambiguity between vulnerability as a general condition of subjects participating in biomedical research or of patients in clinical contexts, and vulnerability as a specific condition of some groups or categories of people, *particularly* exposed to risks of exploitation, manipulation, injustice and injury.

A few years later, in fact, in the 1982 International Guidelines for Biomedical Research Involving Human Subjects adopted by CIOMS, vulnerability is taken into consideration more explicitly as a relevant factor in biomedical research, but it is only in the 2002 version that a more precise definition of vulnerability is rendered, as the incapacity of some subjects to protect their own interests[8]: "Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength or other needed attributes to protect their own interests"[9]. What is important for this analysis, however, is that at the same time the CIOMS guidelines state that vulnerability is a general condition of a lack of power (incapacity to protect one's interests) owing to multiple factors, and refers to it as a *specific* condition of some groups or categories of people, in a supra-individual perspective. Thus, in addition to minors (Guideline 14) and persons not capable of giving valid consent due to mental or behavioural disorders (Guideline 15),the Commentary on Guideline 13 provides an actual list of vulnerable groups: persons in subordinate positions in highly hierarchical contexts ("Examples of such groups are medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police"),elderly persons with forms of senile dementia or who are institutionalised, people receiving welfare benefits or social assistance, poor people and the unemployed, people in emergency departments, ethnic and racial minorities, the homeless, nomads, refugees, prisoners, patients with incurable disease, subjects who are politically powerless ("politically powerless individuals") and members of communities that are unfamiliar with modern medical concepts ("communities unfamiliar with modern medical concepts")[10]. This list, clearly, lacks internal homogeneity, as it can, at most, be taken as an example of a list of cases in which, effectively, the lack of power and the limited capacity to protect one's own interests become particularly relevant.

Such a detailed list of conditions of vulnerability, or conditions in which the risk of vulnerability is higher and significant, is not found in other international documents. Indeed, it is probably the criticism directed at this "categorizing" approach over the years that has led to drastically limit mentioning vulnerable groups explicitly[11]. And so, if already in the UNESCO Declaration on bioethics

[7] NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIOR RESEARCH, *The Belmont Report*, cit., Part C. 3.

[8] On this point, see J.J. VAN DELDEN, R. VAN DER GRAAF, *Revised CIOMS international ethical guidelines for health-related research involving humans*, in *Jama*, 317(2), 2017, pp. 135-136.

[9] CIOMS-OMS, *International ethical guidelines for health-related research involving humans*, 2002, Commentary on Guideline 13.

[10] Ibidem.

[11] For these criticisms see K. KIPNIS, *Seven vulnerabilities in the pediatric research subject*, In *Theoretical Medicine and Bioethics*, 24(2), 2003, pp. 107-120; F. LUNA, *Elucidating the concept of vulnerability: Layers not labels*,

and human rights the reference to vulnerability is linked to the human condition (article 8), and group vulnerability is simply mentioned with reference to particularly vulnerable groups ("groups of special vulnerability") or to groups that are *rendered* vulnerable due to different factors ("groups ... rendered vulnerable by disease or disability or other personal, societal or environmental conditions")[12], in the 2013 Helsinki Declaration the reference to vulnerable groups is entirely generic ("Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm")[13].

However, the reference to group vulnerability has not disappeared from international texts and documents in the field of bioethics, bearing witness to its persistent descriptive capacity, or to its ability to linguistically represent certain contexts subject to protection. For instance, in the Barcelona Declaration on Policy Proposals to the European Commission on Basic Ethical Principles in Bioethics and Biolaw (adopted in November 1998 by Partners in the BIOMED II Project), vulnerability is indicated in itself as a fundamental bioethical principle, alongside autonomy, integrity and dignity[14]. However, in the Report concerning the Declaration, vulnerability is not simply indicated as an inherent characteristic of the human being ("the condition of all life as able to be hurt, wounded and killed"), but is understood as common to all forms of life ("concerns animals and all self-organising life in the world"), and grounds a social responsibility towards life as vulnerable, e.g. by imposing limits on experimentation, and the right to receive the assistance necessary to realise its potential[15].In EU law, for example, the field of biomedical research is one in which the reference to group vulnerability is most frequently used. With more specific regard to legal documents, the 2014 Clinical Trials Regulation[16] at art. 10 (titled "Specific considerations for vulnerable populations") states that for minors, incapacitated, pregnant and breastfeeding women, or other groups or subgroups, specific precautions and procedures are required to obtain authorization for enrolment in a clinical trial. Even if it is not specified what these specific considerations or cautions consist of, this vulnerability still seems to be linked, in an alternative and inevitably ambivalent way, on the one hand to a reduced decision-making capacity, in line with the provisions of the Oviedo Convention on human rights and biomedicine, and with the Additional Protocol on Biomedical Research[17], and on the other hand to an increased risk of suffering damage or injury.

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in *The International Journal of Feminist Approaches to Bioethics*, 2(1), 2009, pp. 121-139; A.S. ILTIS, *Introduction: Vulnerability in biomedical research*, In *Journal of Law, Medicine & Ethics*, 37(1), 2009, pp. 6-11.

[12] https://unesdoc.unesco.org/ark:/48223/pf0000146180 (last visited 02/06/2021)

[13] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last visited 02/06/2021)

[14] P. KEMP, J. DAHL RENDTORFF, *The Barcelona declaration. Towards an integrated approach to basic ethical principles*, in *Synthesis philosophica* 23(2), 2008, pp. 239-251.

[15] *Final Report to the Commission on the Project Basic Ethical Principles in Bioethics and Biolaw*, 1995-1998, http://cometc.unibuc.ro/reglementari/Basic-Ethical-Principles.pdf (last visited 02/06/2021)

[16] *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 Text with EEA Relevance*

[17] COUNCIL OF EUROPE, *Convention for the protection of human rights and the dignity of human beings with regard to the application of biology and medicine*. Oviedo: 1997; ETS no. 164. COUNCIL OF EUROPE. *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning biomedical research*. Strasbourg 2005. CETS no. 195.

In this sense, the Regulation sets out in articles 31-33 particularly stringent guidelines for the acquisition of informed and free consent by minors, incapable subjects (these conditions of vulnerability stem from a reduced ability to safeguard their own interests), or pregnant or breastfeeding women (vulnerability is linked to a situation of increased risk), as well as, in art. 34, for other people who find themselves in contexts of hierarchical or institutional dependency likely to influence their ability to express consent (and therefore, once again, vulnerability is linked to a reduced ability to express *free* consent).With the same oscillation, Recital 15 refers to the condition of vulnerability of "frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders" to encourage the inclusion of these categories in research precisely in order to *limit* their vulnerability[18], and Recital 31 refers to subjects belonging to an "economically or socially disadvantaged group", or to a context of possible manipulation and exploitation as a determinant of vulnerability.

Therefore, although vulnerability in bioethics is a notion as widespread and used as it is ambiguous, it is anything but a useless notion, or mere frill of rhetoric. Quite the opposite: as seen, vulnerability is always linked to specific obligations, duties of special protection and more burdensome procedures. In fact, vulnerability draws attention to the asymmetry of power which inevitably characterizes the clinical context and research in the biomedical field, given the inevitable situation in which patients or trial participants find themselves, with their being *dependent and exposed* towards the medical staff and research teams. In a certain sense, the whole development of the discipline of consent[19], at least within the liberal model, its primary objective was the guarantee of personal autonomy and the symmetrical limitation of vulnerability factors, at least within the perspective of reduced ability to decide for oneself; the growing centrality of consent, in fact, aims to rebalance this asymmetry between doctors or researchers, and patients or trial participants[20].

3. Group vulnerability and the pandemic

The "traditional" enumeration of vulnerable groups, as seen, is based on the idea that some physical, mental or existential conditions can adversely affect health in certain groups of people, either because these subjects are exposed to a *heightened* risk of harm, or because it involves for them a *lower* than standard ability to defend themselves or cope with this risk; Among the factors that can affect the condition of people and groups in this dual direction, there are certainly a number of factors attributable to the category of *situational* vulnerability, that is, to those conditions of vulnerability caused or exacerbated by environmental, political, social, economic factors, and so on. These are factors which can be interrelated with "existential" factors, for example because

[18] On this point see É. GENNET, R. ANDORNO, B. ELGER, *Does the new EU Regulation on clinical trials adequately protect vulnerable research participants?,* in *Health Policy*, 119(7), 2015, pp. 925-931.

[19]On which, in addition to R.R. FADEN, T.L. BEAUCHAMP, *A History and Theory of Informed Consent*, New York, 1986, see also N. EYAL, *Informed Consent, The Stanford Encyclopedia of Philosophy* (Spring 2019 Edition), E.N. ZALTA (ed.) https://plato.stanford.edu/archives/spr2019/entries/informed-consent/ (last visited 02/06/2021); H.T. ENGELHARDT, The Foundations of Bioethics, New York, 1996.

[20] R. ANDORNO, *Is vulnerability the foundation of human rights?* In *Human Dignity of the Vulnerable in the Age of Rights*, Cham, 2016, p. 259

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economically disadvantaged conditions can, together with a not very protective institutional context, produce clinical conditions of fragility or proper pathological conditions; and vice versa, particular health conditions can lead, in certain contexts, to forms of social vulnerability, unemployment and loss of income, or more besides. However, in general, this is a vulnerability that depends on the context and the specific situation in which these subjects find themselves, even if the effects of this vulnerability can vary greatly in intensity depending on the subjective resources, and the degree of resilience of those in that given context[21].

Now, if in general the social determinants of health[22] are factors that influence the conditions of vulnerability of people and groups, it is important to note how, during a pandemic, some of these become particularly relevant and sources of increased vulnerability for specific groups. In other words, specific forms of situational vulnerability depend on the effects of the pandemic on certain groups, due to the pressure exerted on certain social determinants of health. For example, it is known that the act of washing hands frequently is one of the behaviours that more than any other reduces the risk of contagion, the fact that for almost two billion people in the world it is not *materially possible* to put this behaviour into practice represents a primary social determinant of exposure to contagion, and therefore of vulnerability[23]. Therefore, if on the one hand the conditions and social relationships in which people and groups are inserted constitute a known factor in the mortality and morbidity rates of the population, a pandemic acts on these factors by increasing the role these factors play on people's health, and producing outcomes that highlight the inequalities and vulnerable conditions of these groups[24], as well as exacerbating in turn the incidence of these socio-economic factors, in an almost circular way. A pandemic increases the importance of the factors that produce inequalities in relation to the right to health, both because it "aggravates" already unfavourable socio-economic conditions, and because it makes such conditions an obvious risk factor in the exposure to contagion and in the severity of the outcomes[25]. As the UNESCO

[21] On the distinction between intrinsic vulnerability and situational vulnerability, see first, W. ROGERS, C. MACKENZIE, S. DODDS, *Why bioethics needs a concept of vulnerability*, in *International Journal of Feminist Approaches to Bioethics*, Vol. 5, No. 2, 2012, pp. 11-38; and W. ROGERS, C. MACKENZIE, S. DODDS, *Introduction: What is Vulnerability*, cit., pp. 7-9.

[22] The social determinants of health identify the conditions "in which people are born, grow, live, work, and age and the systems put in place to deal with illness" (WORLD HEALTH ORGANIZATION, *Closing the Gap in a Generation: Health Equity Through Action on the Social Determinants of Health. Geneva*, 2008). The literature on the subject highlights how among these determinants there are, for example, education, income, wealth, the type and conditions of work, availability and access to health services, housing, the environment. physical, social environment, and more besides: cf. M. MARMOT, *Medical Care, Social Determinants of Health, and Health Equity*, in *World Medical and Health Policy*, 10 (2), 2018, pp. 195-197.

[23] B. PATTERSON, *PBI Highlights the Importance of the Human Rights to Water and Sanitation During COVID-19 Pandemic. Peace Brigades International-Canada*, 2020 https://pbicanada.org/2020/03/25/pbi-highlights-the-importance-of-the-hrtws-during-covid19-pandemic/ (last visited 02/06/2021)

[24] C.L. MCNEELY, L.A. SCHINTLER, B. STABILE, B., *Social Determinants and COVID-19 Disparities: Differential Pandemic Effects and Dynamics* in *World Medical & Health Policy*, 12(3), 2020, p. 207.

[25] As the WHO points out, "(health equity) exists only when people have an equal opportunity to be healthy. Health inequity, therefore, is the unfair and avoidable difference in health status" (WORLD HEALTH ORGANIZATION, *Closing the Gap in a Generation: Health Equity Through Action on the Social Determinants of Health. Geneva*, cit.): the pandemic, in this sense, is an astonishing factor generating inequalities in guaranteeing the right to health.

International Bioethics Committee correctly pointed out, "Vulnerable individuals become even more vulnerable in times of pandemic. It is particularly important to take note of vulnerability related to poverty, discrimination, gender, illness, loss of autonomy or functionality, elder age, disability, ethnicity, incarceration (prisoners), undocumented migration, and the status of refugees and stateless persons"[26].

Among these factors, the relevance of the economic factor is undoubtedly the most immediately perceptible. The levels of income and distribution of wealth in the population are indeed factors that more directly and evidently influence exposure to the risk of contagion than others, especially in the interaction with other elements[27]. The scarcity of economic resources can in fact affect exposure, access to healthcare, the possibility of receiving assistance, and the subject's own social behaviour (for example, in the effective possibility of limiting travel, or taking advantage of home working)[28] In this sense, for example, some authors have identified social housing residents, single-parent families and low-income populations as being at greatest risk during a pandemic. With limited financial resources and unstable income, such groups include people who may be forced to live in inadequate housing, i.e. with inadequate and crowded sanitation facilities[29], both factors that increase the risk of exposure during an epidemic. Similarly, many studies have shown that some income bracket may have no alternative to using public transport, which in turn is an important source of exposure to the contagion[30]. In a similar sense, the conditions and the type of work are factors that influence exposure to the contagion during a pandemic; for example, occupations that involve physical proximity (care jobs, domestic work, public transport), and which in turn are prevalent among the population groups with more limited economic resources, represent an element of strong exposure and an increased risk of contagion[31]not only that, but the risk of worse or fatal outcomes in the course of the disease is related to factors such as a worse state of general health, the presence of cardiovascular and liver diseases, diabetes and cancer, all conditions which have an inversely proportional relationship to the socioeconomic conditions of the population[32].

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[26] UNESCO – IBC, *Statement on COVID-19. Ethical consideration from a global perspective*, 2020 https://unesdoc.unesco.org/ark:/48223/pf0000373115 (last visited 02/06/2021)

[27] In relation to the Covid19 pandemic see A. BANIK, T. NAG, S.R. CHOWDHURY, R. CHATTERJEE, *Why Do COVID-19 Fatality Rates Differ Across Countries? An Explorative Cross-country Study Based on Select Indicators*, In *Global Business Review*, 2020:0972150920929897-.

[28] E. VAUGHAN, T. TINKER, Effective health risk communication about pandemic influenza for vulnerable populations, in American Journal of Public Health, 99(S2), 2009, S324-S332; G. IACOBUCCI, Covid-19: Deprived areas have the highest death rates in England and Wales, in BMJ, 2020, 369; S. DREFAHL, M. WALLACE, E. MUSSINO, ET AL., *Sociodemographic risk factors of COVID-19 deaths in Sweden: A nationwide register study*, Stockholm Research Reports in Demography, 2020, 23.

[29] M. WALLACE, H.M., LIESL, G.C. KATHRYN, ET AL., *COVID-19 in Correctional and Detention Facilities — United States, February–April 2020*, in *MMWR Morb Mortal Wkly Rep*, 2020, 69 (early release).

[30] This element has been highlighted in relation to past flu epidemics; see for example P. BLUMENSHINE, A. REINGOLD, S. EGERTER, ET AL., *Pandemic influenza planning in the United States from a health disparities perspective*, in *Emerging Infectious Diseases*, 14(5), 2008, pp. 709-715.

[31] B. Burström, W. Tao, *Social determinants of health and inequalities in COVID-19*, in *European journal of public health*, 30(4), 2020, pp. 617-618.

[32] I. SOMMER, U. GRIEBLER, P. MAHLKNECHT, ET AL., *Socioeconomic inequalities in non-communicable diseases and their risk factors: an overview of systematic reviews*, in *BMC Public Health*, 15, 2015, p. 914.

The economic factor, and in general unfavourable socio-economic conditions, are elements intertwined with other factors in determining conditions of vulnerability for particular social groups, such as for example ethnic minorities. The lower levels of education, socioeconomic status, worse housing conditions, and obviously less insurance coverage (especially in contexts where health care is not universal) and worse access to health services[33], in fact, they significantly contribute to determining higher rates of morbidity and mortality among these groups compared to the "general" reference population[34]. If this is generally true, the conditions linked to the pandemic exacerbate the incidence of these factors, and lead to greater vulnerability in terms of both exposure to risk and severity of outcomes for those belonging to these groups[35]; for similar reasons, a higher incidence of infections has been verified among people belonging to ethnic minorities and economically disadvantaged sections of the population, generally employed in sectors such as catering and healthcare in which the exposure to risk factors is greater, or personal care and service work that is incompatible with effective social distancing.

Other vulnerability factors emerging from the pandemic relate to health literacy, or barriers to accessing health services. Regarding the first factor it can be noted that the degree of competence and awareness with which people obtain, receive, and evaluate the information, in order to make competent decisions on health matters, is linked to the general level of education and ability to use information technologies; these skills are present in an inversely proportional measure to the socio-economic level of the subjects, and are often very lacking in groups such as ethnic minorities, irregular migrants, the elderly. These groups, therefore, and to the extent that health literacy is crucial in determining competent choices and behaviors in health matters, become vulnerable in the context of a pandemic precisely on account of the combined effect of multiple factors increasing the exposure to risks[36]. As for the second factor, it has unfortunately been known for some time that access and use of health services can be particularly burdensome for specific groups, due to language barriers, poor knowledge of bureaucratic procedures and mechanisms, fewer relational support networks, or directly xenophobic attitudes in the community of residence[37]; all these, and more, are factors that, by limiting or hindering access to health services, represent conditions of vulnerability for specific groups (for example, newly established migrant communities) in relation to the health emergency and the ability to face up to it.

[33] F. Macioce, *The Right to Accessible and Acceptable Healthcare Services. Negotiating Rules and Solutions With Members of Ethnocultural Minorities,* in *Journal of bioethical inquiry*, 16(2), 2019, pp. 227-236.

[34] B. Thomas, *Health and Health Care Disparities: The Effect of Social and Environmental Factors on Individual and Population Health*, in *International Journal of Environmental Research and Public Health*, 11, 2014, pp. 7492–7507.

[35] S. Yaya, H. Yeboah, C. H. Charles, A. Otu, R. Labonte, *Ethnic and Racial Disparities in COVID-19-Related Deaths: Counting the Trees, Hiding the Forest*, in *BMJ Global Health*, 2020, 5:e002913. ; see also J.H. Farley, J. Hines, N.K. Lee, et al., *Promoting Health Equity in the Era of COVID-19*, in *Gynecologic Oncology*, 158(1), 2020, pp. 25-31.

[36] S. Van den Broucke, *Why health promotion matters to the COVID-19 pandemic, and vice versa*, in *Health promotion international*, 35(2), 2020, pp. 181-186.

[37] B. Rechel, P. Mladovsky, D. Ingleby, J.P. Mackenbach, M. McKee, *Migration and health in an increasingly diverse Europe*, in *Lancet*, 381(9873), 2013, pp. 1235-1245; L. Montesi, M.T. Caletti, G. Marchesini, *Diabetes in migrants and ethnic minorities in a changing World*, in *World Journal of Diabetes*, 7(3), 2016, pp. 34-44.

In the opposite sense, it is interesting to note how the Sars Cov 2 virus has altered the horizon of group vulnerability, as it were. Groups traditionally considered as vulnerable seem to show particular resilience to the virus, in a way that is not entirely expected and predictable: very young children, for example, do not represent a particularly vulnerable group in the current context of the pandemic, as significant rates of morbidity and mortality have not been shown[38], compared to other far more vulnerable groups. Similarly, pregnant women, normally considered vulnerable to other viral infections (chickenpox, measles, other influenza viruses), being likely to have negative health consequences for the foetus (such as influenza H1N1 or Zika), do not appear to be exposed, in a significant way, to the risks associated with the Sars Cov 2 virus[39].

4. Trials and informed consent: the case of vulnerable groups

The issue of group vulnerability has assumed particular relevance in the context of the pandemic not only because, as mentioned, both the pandemic itself and the restrictions put in place to limit contagion have *generated* new forms of group vulnerability, or *aggravated* pre-existing conditions of vulnerability. Group vulnerability has also gained importance in relation to a more "traditional" context, so to speak, namely in relation to health treatments, and to participation in trials aimed at developing vaccines; what emerges - in a manner consistent with prominent bioethical principles in this area - is the need for the provision of additional precautions and reinforced safeguards in the context of research, in relation to the risks to which people belonging to groups identified as vulnerable are exposed.

As Van Delden[40] rightly notes, if the vulnerability is situational, similarly precaution and forms of protection should be shaped for the specific case, beyond pre-established paradigms and the risk of labelling. In this line, the prospective change adopted in the CIOMS Research Guidelines appears very reasonable, since the traditional approach based on the *preventive* identification of vulnerable groups is replaced by an approach based on case analysis: "The account of vulnerability in this Guideline seeks to avoid considering members of entire classes of individuals as vulnerable. However, it is useful to look at the specific characteristics that may render individuals vulnerable, as this can aid in identifying the special protections needed (…) Different characteristics may also co-exist, making some individuals more vulnerable than others. This is highly dependent on the context"[41].

On the one hand, group vulnerability is therefore context-dependent, and cannot be deduced prejudicially from the common characteristics of a group of people (minor age, economic status, etc.) participating in research. On the other hand, the fact that vulnerability must be detected by

[38] L. SOMINSKY, D.W. WALKER, S.J. SPENCER, *One size does not fit all - Patterns of vulnerability and resilience in the COVID-19 pandemic and why heterogeneity of disease matters*, in *Brain, behavior, and immunity*, 87, pp. 1-3.

[39] However, for some risks, see S.A. RASMUSSEN, ET AL., *Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know*, in *American Journal of Obstetrics and Gynecology*, 2020 doi: 10.1016/j.ajog.2020.02.017.

[40] J. VAN DELDEN, R. VAN DER GRAAF, *Revised CIOMS international ethical guidelines for health-related research involving humans*, in *Jama*, 317(2), 2017, p. 135.

[41] CIOMS-OMS, *International Ethical Guidelines*, cit., Guideline 15, p. 47.

induction from the analysis of actual cases does not mean that it is reduced to the *individual* dimension, or that it is not possible to speak of vulnerable groups or to postulate their existence; the group dimension of vulnerability remains, but it must be understood as a *presumptive* element, as a fact that must be verified in practice, and which can be denied in the context. However, this is, once again, a fact that - on this level of mere presumption - brings together groups and categories of people, placing them in a similar way in a condition of increased risk in relation to participation in a *specific* clinical research. And so, the condition of people living in old people's homes or psychiatric hospitals, or people in prison, is a condition which places these subjects up against a greater risk, if enrolled in clinical research, related to the possibility that their inclusion in an environment which is *intrinsically coercive* affects their freedom to express consent. Or again, women can be considered a vulnerable group if the specific circumstances in which they live (a cultural, family or social context in which manifestation of their will is bound to authorization by the spouse or father) and the specific characteristics of the research place them in a severely limiting condition regarding manifestation of consent and the possibility of exercising control over their own choices.

Returning to previously mentioned examples, people living in poverty or the homeless, or people receiving welfare benefits and social assistance can be considered vulnerable, if the specific conditions in which they live (for example, the limitations they encounter in accessing health care), and the modalities of the research, suggest the presence of constraints and a limited freedom in decision-making[42].

If this paradigm is applied to the current context, therefore, it is the specific task of those conducting research to foresee and model specific forms of guarantees for groups that *in the pandemic context* can be considered vulnerable, so that there are no more than minimal risks involved for procedures that offer no direct benefits for research participants; and it is always up to them to verify that research is conducted only when it refers to conditions specifically affecting these groups. The problem is that, in the context of the pandemic, the identification of vulnerable groups, and therefore of the subjects for whom precautions and additional forms of protection are required, not only cannot be solved by referring to pre-established classifications, but it presents unprecedented difficulties: in fact, in it not only are many conditions of vulnerability exacerbated, but new vulnerabilities emerge (with additional difficulties, precisely due to this novelty, in detecting them and understanding their dimensions and characteristics), and the factors that these vulnerabilities determine or aggravate intersect in unprecedented ways.

Consider, for example, the case of the elderly, who, as we have seen, can be identified as a particularly vulnerable group in the context of the Covid-19 pandemic, due to the high mortality and morbidity rates recorded in this segment of the population; and yet, considering this group as particularly vulnerable can lead to exclusion of the people belonging to it from enrolment in clinical trials[43]. If this is what has happened in some recent vaccine trials[44], the effect of this exclusion tends

[42] These are all examples included in the same CIOMS Guidelines in the commentary to Guideline 15.

[43] In fact, it is known that some groups traditionally considered as vulnerable (minors, the very elderly, people in detention, pregnant women, etc.) tend to be substantially excluded from research, or in any case their participation in research takes place in compliance with far more stringent and limiting conditions.

[44] B.K. HELFAND, ET AL., *The exclusion of older persons from vaccine and treatment trials for coronavirus disease 2019 —missing the target*, in *JAMA Internal Medicine*, 180(11), 2020, pp. 1546-1549.

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to increase the vulnerability of this group, rather than reduce it, because it produces an important lack of data and analyzes on efficacy, dosages and side effects on a group of patients which, paradoxically, is one of those most affected by the virus and suffers its effects most severely.

Similarly, the exclusion or severely limited participation in transnational trials of people residing in economically depressed areas or with very low per capita income stems from excellent reasons linked to doubts concerning the quality of the procedures for informed consent and effective freedom of individual choice, on the presence of a "double standard" regarding the use of placebo[45], on the availability of treatment and post-trial care, the absence or weakness of norms and local institutions that can protect the interests and dignity of individuals with regard to the commercial interests of those who fund research, and so on[46]. Such arguments, as mentioned, are more than reasonable[47], and moved by consideration of the specific condition of vulnerability of populations in developing countries: the idea that Africa, to put it plainly, should not be a kind of haven for under-regulated trials, within a para-colonialist paradigm , makes perfect sense[48]. And yet, the strong limitations and cautions linked to this vulnerability are likely to bring about, in the context of the pandemic, further, unintentional vulnerabilities for these very same populations: as different researches have pointed out, vaccine trials could as a result fail to take adequate account of important factors in the evaluation of immune response and disease course, for example to the extent that these are influenced by genetic variants[49]. The justified concern for the (economic, infrastructural) vulnerability of certain populations can in short generate, if absolute, new vulnerabilities, or, at least, may not lead to desired outcomes, but rather worsen the conditions of the populations involved; if, as already noted in other contexts, ethnicity can influence immune responses and the effectiveness of vaccines, the exclusion of African countries from the trials could expose these populations to greater risks, as unintended consequence[50].

In this context, in which the "traditional" conditions of vulnerability are modified or intertwined with other and new conditions determined by the pandemic, it is important that the tools for mitigating

[45] See for instance P. DE ZULUETA, *Randomised placebo-controlled trials and HIV-infected pregnant women in developing countries. Ethical imperialism or unethical exploitations?,* In *Bioethics*, 15, 2001, pp. 289-311.

[46] On these perplexities and risks, see M. ANGELI, *The ethics of clinical research in the third world*, in *N Engl J Med* 337, 1997, pp. 847-849; H. VARMUS, D. SATCHER, *Ethical complexities of conducting research in developing countries*, in *N Engl J Med* 337, 1997, pp. 1003-1005; see also F. LUNA, *Research in developing countries*, in B. STEINBOCK (ed.), *The Oxford Handbook of Bioethics*, New York, 2007, pp. 621-647.

[47] Even though, as clearly explained in the CIOMS International Ethical Guidelines for Health-Related Research Involving Humans, this paucity of resources and low level of income cannot be understood as a "local" factor, that is, linked exclusively to economically disadvantaged areas and countries: "Low-resource settings should not be interpreted narrowly as low-resource countries. These settings might also exist in middle- and high-income countries. Moreover, a setting can change over time and no longer be considered low-resource" (Guideline 2).

[48] The WHO Director General expressed this concern explicitly: *Coronavirus: Africa will not be testing ground for vaccine, says WHO*, in *BBC*, 6 April 2020 https://www.bbc.com/news/worldafrica-52192184. (last visited 02/06/2021)

[49] Much research is currently underway on the role of genetic variants in Covid19. See, for an overview, D.J. BURGESS, *Host genetics of coronavirus infection*, in *Nature Reviews Genetics*, 2021, 22(1) https://doi.org/10.1038/s41576-020-00310-y (last visited 02/06/2021)

[50] On this point, J.A. SINGH, *The Case for Why Africa Should Host COVID-19 Candidate Vaccine Trials, Perspective*, in *The Journal of Infectious Diseases*, 2020, 222 (3), pp. 351-355.

the vulnerability itself are in turn modelled taking this context into account, and the specific conditions and forms of vulnerability of each group. From this point of view, the procedures for obtaining informed consent, that specifically represent one of the most typical tools of "empowerment" of the person undergoing health treatments, must be modelled in such a way as to make them not only effectively capable of vehicling the necessary information in a specific context, but also suitable, for each group of people, to make the care and protection *needs* linked to the specific condition of vulnerability emerge.

On the one hand, it is certainly true that the procedures for obtaining consent are in themselves tools for mitigating vulnerabilities, as they reduce the margins within which people are at risk, owing to their vulnerability, to be manipulated, exploited, deceived, or in any case exposed to the pressure of uncontrollable factors[51]. And above all, the fact that information must be provided in a *modality appropriate* to the conditions of the person whose consent is being sought[52] is an indication that the vulnerability factors should not be considered abstractly, but starting precisely from the concrete situation, from the specific conditions of vulnerability to which a person is exposed.

On the other hand, the fact that in the pandemic context the vulnerabilities are not only - as always - situational, but also largely unprecedented, makes it necessary to rethink consent in a relational direction, that is within communicative contexts, whose form, modality, and incidence are adequately taken into account[53]. The process of informed consent, in short, must be modulated taking into account, in addition to its information content, the context within which it is implemented, the power relations, the symbolic and discourse contexts that support and shape it[54], since all this gives shape to people's real possibilities to make choices, and their real possibilities to exercise personal freedom. In this direction, consideration of the conditions of vulnerability associated with certain groups - understood as an ensemble of people placed in a similar *position* in relation to determined risk factors - is crucial precisely because it allows the emergence and visibility of the specific needs of those people belonging to it, both in communicative and relational terms.

For example, in the context of the procedures for obtaining consent to participate in a trial, it is necessary - *in addition to* information on the risks and benefits, and any other information that the main national and international regulatory instruments rightly require[55]- that there should also be consideration of subjective perceptions in relation to the efficacy of the object of the trial, or

[51] For a comment on this model, see J. ANDERSON, A. HONNETH, *Autonomy, Vulnerability, Recognition, and Justice*, in J. ANDERSON, J. CHRISTMAN (eds.), *Autonomy and the Challenges to Liberalism, New Essays*, Cambridge, 2005, p. 130.

[52] Law 219/2017 art. 1 paragraph 4: "Informed consent (is) acquired in the ways and with the tools most suited to the patient's conditions".

[53] Contrary to what happens today, within models that place consent in an ethically neutral perspective: O. CORRIGAN, *Empty ethics: the problem with informed consent*, in *Sociology of Health & Illness*, 25(3), 2003, p. 770.

[54] O. CORRIGAN, *Empty ethics*, cit.: "this process is not situated outside the realm of power, but rather such decisions are made in contexts where prevailing discourses and norms shape the field of freedom and choice", p. 771.

[55] In the Oviedo Convention, for example, see arts. 5 et seq, but also 10 (on the right to information), 16 (on participation in experiments), 19 (on donation and transplants), 1997 https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164. (last visited 02/06/2021)

healthcare professionals' required knowledge[56], the role and involvement of family members, the expectations regarding the type of relationship between patient and researcher, role played by the institutions to which reference is made and which promote research, and many other factors[57]. But beyond that it is necessary to take into account those specific needs that vulnerable groups manifest, and which are not reduced to the many, and variable, individual interests: a vulnerable group does not simply manifest interests that are more or less reasonable, but needs that are unmet and determine specific conditions of vulnerability in a given context. For example, the vulnerability of "the very elderly" in the context of the pandemic cannot be reduced to the level of individual interests of patients, in relation to the information which may be needed due to the relational context in which they are placed, which the healthcare and research personnel must take responsibility for within the framework of the information process; the vulnerability of this group is also related to specific *common* conditions (on a clinical and epidemiological level, for example) which the subjects are not necessarily aware of, and which nevertheless determine specific information, relational, and care needs. In this sense, communication within informed consent processes cannot prescind from the consideration of the vulnerability of groups, as well as individuals, because only at this level is it possible to build *inclusive* information and communication processes, in which the need for protection and care stemming from the common positioning of subjects belonging to a group or category obtain an adequate response.

All of which, obviously, implies that the communication process cannot be conveyed by a form, or reduced to a series of information conveyed in a *top-down* direction, and least of all that such information can be standardized in models valid for everyone, because, as already stated, it depends on the context, on the relevant relationships in that particular case, on the subjects involved, and on the common needs of specific groups. These are elements that set aside, at least to a certain extent, the subject of the communication and its informational content, and highlight instead the point of view of the *methods* of communication, and the people involved in the communication process; but above all these are elements that can only be adequately assessed within a communicative context characterized by trust and entrustment.

The information underlying the consent must, therefore, be devised *in the context* of the relationship between doctor and patient, or researcher and trial participant; that is, they should not be thought of as something that is transferred from one subject to another - and which, therefore, pre-exists the relationship - but as something that is produced within the relationship itself, due to the characteristics and purposes of the participants in the interaction[58]. The information is therefore not

[56] For a review, see M. MURSHID, Z. MOHAIDIN, G. YEN NEE, *The influence patient's characteristics "requests and expectations" on physician prescribing behavior: A review*, in *International Journal of Pharmaceutical and Healthcare Marketing*, 10(4), 2016, pp. 390-411; K. WEINFURT, ET AL., *The correlation between patient characteristics and expectations of benefit from Phase I clinical trials*, in *Cancer*, 98(1), 2003, pp. 166-175.

[57] P. BIELBY, *Towards supported decision making in biomedical research with cognitively vulnerable adults*, in O. CORRIGAN ET AL. (Eds.), *The limits of consent: A socio-ethical approach to human subject research in medicine*, Oxford, 2009, p. 153.

[58] On this aspect, see N.C. MANSON, O. O'NEILL, O., *Rethinking Informed Consent in Bioethics*, Cambridge, 2007, p. 32; see also, for a broader analysis of the relationship between informed consent and vulnerability, F. MACIOCE, *Between Autonomy and Vulnerability. Rethinking Informed Consent in a Relational Perspective*, in *Notizie di POLITEIA*, XXXV, 134, 2019, pp. 111-128.

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adapted and relevant in abstract terms, or in relation solely to the patient's clinical condition, but it is adapted in terms of what the participants in the interaction do, think, expect, deem to be important, and in terms of the wider context within which they are placed. Consent is *informed* not only as regards the quantity and quality of the information that is exchanged, but also as to the modality and relational context within which this exchange takes place.

What makes the information truly adequate, in other words, is the relationship of trust that is established between speakers, and the consistency of their methods of interaction and dialogue with the affirmation and preservation of trust. Negatively, this also means that communication can fail not only on account of the quantity and type of information that is conveyed, but also on account of the way in which the participants in the communication interact; and consequently, regardless of the quantity, adequacy and relevance of the information, the outcome of the communication may strengthen the patient's vulnerability, despite having - as a merely theoretical possibility - guaranteed autonomy. In short, what guarantees the person, and reduces their vulnerability, is not the quantity or quality of information they receive (an important element in any case), but the dialogical relationship with the other, with the doctor or healthcare personnel, which constitutes the basis for a relationship of trust *within which* the person expresses his/her consent.

In the context of the pandemic, the role of trust is certainly very relevant[59], perhaps even more than it already normally is. On the one hand since, as is easily understandable, a pandemic affects the relationship of trust between rulers and ruled (with respect to the effectiveness of the contagion containment measures, the management and tracking of contacts, the information which is communicated through the media, and so on); on the other hand given that, in the face of a new virus, the investment of trust that is required of the whole community concerns the entire process of trials and mass vaccination and involves public institutions, research bodies, healthcare institutions, pharmaceutical companies, and others. In short, it involves systems and actors much broader and more complex than those normally involved in a clinical trial, in a context of urgency and with variables, therefore, being less controllable. Thus, as the Nuffield Council correctly pointed out in a recent statement on pandemic management health policies, "trust is essential in order to maintain support on the part of the general public for the measures proposed: without such trust, compliance with those measures is likely to be low"[60].

In this sense, clear, transparent and reliable communication of the "measures" adopted and the justifications that support them, as well as the risks and uncertainties of faster than usual trials, takes absolute priority not only for the health personnel directly involved, but above all for public institutions. Discussing on the media in a confused, non-transparent, and often contradictory manner - which unfortunately has happened in some European countries, is certainly a choice that does not contribute to building a relationship of trust between citizens and public institutions. It is equally important, however, that public institutions play a primary role in communicating with patients and people involved in the trials, or rather that the onus of providing information is not left entirely to

[59] A. Dawson et al., *Key ethical concepts and their application to COVID-19 research*, in *Public Health Ethics*, 13(2), 2020, p. 127-132.

[60] Nuffield Council of Bioethics, *Ethical considerations in responding to the COVID-19 pandemic*, 2020, p. 3

research teams: the specific conditions determined by the pandemic, and in particular the need for a mass vaccination campaign, entail that the communication and information needs of vulnerable groups are met in a perspective consistent with generally changed conditions. The measures adopted to deal with the pandemic, as well as the specific methods of managing the trials, represent a significant, and incredibly rapid, paradigm shift on a cultural level, because they have determined a shift of the cornerstone of clinical ethics from "the single individual -patient to the public interest". And it is necessary that public institutions - protagonists in taking decisions in the context of the pandemic –underline how this step involves no conflict between individual and collective interests; on the contrary, what stems from the adoption of a "relational perspective", on the basis of which a person's autonomy "always" manifests itself (not only during pandemics) within networks of social relations, and that individuals, insofar as they are internal to this system of relations, have interests that are not distinct from those of society as a whole[61].

5. Conclusions

As mentioned in these pages, if we want to prepare adequate forms of protection and orient research procedures and practices in order to guarantee the dignity and rights of people in vulnerable conditions, it is crucial to identify the factors that can produce or aggravate such conditions in the context of the pandemic. Indeed, it is important to consider, on the one hand, that a pandemic affects the conditions of vulnerability of individuals and groups, for example due to the pressure exerted on certain social determinants of health; on the other hand, it should be emphasized that the pandemic has somehow *altered* the horizon of group vulnerability, in such a way as to make *traditional* vulnerability categories not applicable, or at least not in an automatic way.

In the context of research, and especially in relation to participation in trials aimed at the development of vaccines, there is therefore a need for specific precautions to be put in place with regard to the risks to which people belonging to groups identified as vulnerable are exposed, and therefore those conducting the research are to provide such guarantee tools for those who, *in the context of the pandemic*, can be considered as particularly vulnerable; all this, as mentioned, even where identification of these vulnerable conditions proves to be particularly complex, given the new way in which the effects of the pandemic interact with more known and typical elements of vulnerability.

In this context, it is essential that in the procedures for obtaining consent to participate in a trial, not only is the relevant information to be provided, but consideration is also to be given to subjective

[61] On the relational perspective, with reference to autonomy and consent, see J. ANDERSON, *Autonomy and Vulnerability Entwined*, in C.A. MACKENZIE, W. ROGERS AND S.M. DODDS (eds.), *Vulnerability. New Essays in Ethics and Feminist Philosophy*, New York, 2014, pp. 134-161; M. FRIEDMAN, *Autonomy in Social Context*, in C. PEDEN AND J.P. STERBA (eds.), *Freedom, Equality, and Social Change*, Lewiston, New York, 1989, pp. 158-169; C.A. Mackenzie, N. Stoljar, *Autonomy Refigured*, in C.A. MACKENZIE, N. STOLJAR (eds.), *Relational Autonomy: Feminists Perspectives on Autonomy, Agency, and the Social Self*, New York, 2000; N.C. MANSON, O. O'NEILL, O., *Rethinking Informed Consent in Bioethics*, Cambridge, 2007; D.T. MEYERS, *Self, Society and Personal Choice*, New York, 1989.

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perceptions and expectations, and the role of the institutions to which reference is made, and which promote research; above all, it is necessary to take account of the specific needs (of an informative type, but also of a social and relational type) that vulnerable groups manifest, and which are not to be reduced to the many, variable, individual interests.

To this end, the role of public institutions is crucial; only if, *alongside* the health personnel and research teams, public institutions carry out a task that is as informative as it is supportive, consent will be based not only on adequate information, but on interpersonal trust (towards health personnel) and systemic trust (towards institutions), so as to make it effectively expressive of the individual's autonomy. The investment of trust required of the community, and related both to the containment measures and to the timeframe and trail methods, as well as to the prioritization criteria for mass vaccination, in fact, involves public institutions, research bodies, health institutions, pharmaceutical companies, and all the actors involved in these processes; only if people perceive that their needs (as individuals and as groups) are adequately considered by them all, will the consent they manifest truly express their autonomy and willingness to participate in research.

Special issue

Clinical trials in the time of a pandemic: implications for informed consent

Laura Palazzani*

ABSTRACT: Focusing on clinical trials in the time of a pandemic, the contribution offers a comprehensive overview of the main challenges for investigators-physicians and patient-participants, discussing their ethical implications for the informed consent. Namely, adaptive and pragmatic trial designs can balance the rapidly changing standards of care with speed and agility, but these are designs which encompass specific implications for the informed consent process; the move towards the use of off-label drugs and compassionate pharmaceuticals in pandemics, which has been unavoidable due to the urgency of treating patients and the lack of knowledge on the virus, on the other hand raises many ethical questions that should be carefully addressed; the impact of the pandemic on ongoing clinical trials and on new trials, due to Covid-19 restrictions, needs proper consideration as well. Moreover, the contribution discusses the ethical conditions for deferred consent and key elements of re-consent alongside with ethical issues related to an electronic-digital consent in the case of tele-medicine and remote information-monitoring. Finally, the article encompasses a focus on patients' vulnerabilities, including specific vulnerabilities (age, gender and ethnicity) that should be protected in conducting clinical research.

KEYWORDS: Adaptive trials, deferred consent, informed consent, off-label use of drugs, re-consent

SUMMARY: 1. Covid-19 and new challenges to clinical trials and informed consent – 2. The absence of a "standard of care" in adaptive and pragmatic trials: a dynamic-flexible consent – 3. Off-label and compassionate use as trials: a gradual-accompanied consent – 4. Possible alternatives: re-consent – 5. Deferred consent as exception for informed consent and the role of Ethics Committee – 6. Tele-medicine and remote information-monitoring: an electronic-digital consent – 7. Restrictions and changes of protocols: informed consent and additional risks – 8. Clinical trials and patient's vulnerabilities – 9. Specific vulnerabilities: age, gender, ethnicity.

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1. Covid-19 and new challenges to clinical trials and informed consent

In the field of bioethics and international bio-law, the centrality of informed consent is a value that can now be considered acquired and undisputed. The bioethical discussion is about 'how' to inform[1], certainly not about "whether" to inform, since the doctor's duty to inform and the patient's right to be informed has matured in the context of ethical, deontological and legal debate[2]. Requirements for "good" informed consent in clinical trials are: explanation of the method and objectives of the research, duration and number of participants, enrollment criteria, research method and modality of carrying out the research, description of the direct and indirect benefits and risks, revocability of consent, possibility of interruption of the research[3]. During a pandemic the duty to inform and the right to be informed remain crucial on an ethical, deontological and legal level and, in conditions of emergency care/ treatment (in the absence of therapies) and scarcity of resources to provide treatment (physicians), become even more challenging; in the context of the pandemic emergency, the information process (and therefore, consent) presents some sensitive ethical issues. Very few are the traditional ethical requirements that can be fulfilled in this context, because of the urgency and emergency, unclear or changing methodology, open enrollment (with very few exclusion criteria[4]), uncertainty of benefits and risks, high probability of interruption of research.

Despite the urgent need for rapid advances in Covid-19 treatment, the ethical imperative to obtain informed consent remains[5]. Valid informed consent for research participation requires both adequate disclosure of the key features of the research, including information relevant to the condition and the intervention offered, and adequate comprehension of that information and a voluntary decision to participate by the person giving consent. A number of factors, however, complicate both sides of this equation in the emerging field of Covid-19 clinical research. It is

[1] The i-CONSENT Guidelines address the issue of informed consent process, with the specific perspective of tailoring the information to specific target groups. Basing on an ethical and legal review of international documents and guidelines, the Guidelines include also three fact sheets on informed consent in biomedical research in the COVID-19 pandemic context. See I-CONSENT CONSORTIUM, *Guidelines for Tailoring the Informed Consent Process in Clinical Studies*, Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (FISABIO), Generalitat Valenciana, 2021, https://i-consentproject.eu/wp-content/uploads/2021/03/Guidelines-for-tailoring-the-informed-consent-process-in-clinical-studies-2.pdf. (last accessed June 9th, 2021).

[2] See L. PALAZZANI, *Informed Consent, Experimentation and Emerging Ethical Problems*, in *BioLaw Journal-Rivista di BioDiritto*, 1/2019, pp. 11-22.

[3] Council of International Organizations of Medical Science (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf (last accessed June 9th, 2021).

[4] The Italian Committee for Bioethics tackles this issues in the Opinion "Biomedical research for novel therapeutic treatments within the Covid-19 Pandemic: ethical issues", October 22nd, 2020, http://bioetica.governo.it/en/opinions/opinions-responses/biomedical-research-for-novel-therapeutic-treatments-within-the-covid-19-pandemic-ethical-issues/ (last accessed May 31st 2021); see also M. JANSEN, P. ANGELOS, S. SCHRANTZ ET AL., *Fair and equitable subject selection in concurrent COVID-19 clinical trials*, in *J Med Ethics*, September 2020.

[5] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, Guideline 23 "Research in an emergency context".

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necessary to consider several challenges for investigators-physicians and patient-participants, and implications for informed consent.

Given the novelty of the virus, there is profound uncertainty about the nature of Covid-19, its impact on humans, and best therapies. The Covid-19 pandemic has presented unique challenges for the clinical trial community, both in the rapid establishment of Covid-19 clinical trials and many existing non- Covid-19 studies either being temporarily paused (whether that is a complete pause or pause in some activities) and/or adapting their processes[6]. Research is evolving day by day, with new information on epidemiological transmission, symptomatology, the determination of risk. This rapid change makes it difficult to assess the potential impact of research on therapies, determining which drug mechanisms of action may be promising, and how different types of drugs may interact with each other.

In consideration of patients' critical conditions, some Covid-19 trials allow the inclusion of patients in their protocols on the basis of the so-called "deferred consent" or "exemption from informed consent", used in emergency-care research settings; this is possible, according to international ethical and legal regulations, following specific ethical conditions that will be discussed in this paper, alongside with the issue of re-consent (identified as an action in which a subject, or representative, makes a decision about whether to re-affirm a previous choice of clinical trial to participate in research.

One of the basic elements for informed consent is the description of any risks or discomforts to the subject, the lack of knowledge on Covid-19 research makes it difficult to assess how experimental drugs, may affect subjects, even when such interventions are approved for other indications and significant previous knowledge regarding their safety has been obtained in non-COVID populations.

2. The absence of a "standard of care" in adaptive and pragmatic trials: a dynamic-flexible consent

The so-called "research exceptionalism" is the view that key features of rigorous research, like randomization, double blind, or placebo comparators, conflict with clinicians' care obligations. In Covid-19 pandemics no study participant receives a "standard of care", because there is no standard of care known, and there are no alternatives for participants to the pharmaceuticals used for trials. In a context, such as the present pandemic, where there is no cure and no vaccine, the ethical imperative is to save lives with any potentially effective treatment, including those that are only empirical or unproven. Every possibility, even intuitively potentially beneficial, should be tried, and

[6] E. MITCHELL ET AL., *It is unprecedented: trial management during the COVID-19 pandemic and beyond*, Trials (2020) 21:784. On the impact of the COVID-19 pandemic on clinical trials, see also J. HASFORD, *Impact of the COVID-19 pandemic on clinical trials with drugs*, in *Expert Opinion on Drug Safety*, vol. 19, n. 11 (2020), pp. 1373-1375; T. PEREZ ET AL., *Conducting Clinical Research in the Era of Covid-19*, in *The American Journal of the Medical Sciences*, vol. 360, no. 3, Sept. 2020; H.G. EICHLER, M. CAVALERI, H. ENZMANN, F. SCOTTI, B. SEPODES, F. SWEENEY, S. VAMVAKAS, G. RASI, *Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?*, in *Clin Pharmacol Ther*., vol. 108, no. 4, October 2020, pp. 730-733; A.G. SINGH, P. CHATURVEDI, *Clinical trials during COVID-19*, in *Head & Neck*, 2020, pp. 1–3.

object of a trial. Implementing and accelerating Covid-19 clinical trials is the only way to improve treatment[7]: trials are treatments in themselves.

The absence of a "standard of care" makes participation in a clinical trial for a Covid-19 treatment the only way to receive / obtain /identify a (potential) cure/treatment. While the pandemic is rapidly evolving, there is no specific treatment available for patients with Covid-19. Current clinical practice is mainly based on supportive care as mechanical ventilation and treatment of secondary infections. In this specific context, randomized controlled trials are ethically controversial when offering participants randomization into a placebo arm that could produce serious harm including additional suffering, or even death. Adaptive and pragmatic clinical trial designs are the only methodological alternative, even if ethically challenging.

The rapid action from concept to implementation of clinical studies is crucial during infectious disease outbreaks. Adaptive COVID-19 trials are designed with multiple investigational therapies, that can be compared to identify subgroups of patients who respond best to them[8]. Pragmatic trials may evaluate therapies in a wider range of patients with the disease. The point of departure should be expert opinion, preliminary data of basic preclinical laboratory studies, case reports, and observational studies. Pandemics require an agile and flexible investigational approach (compared to the rigor and inflexibility of randomized control trials), obtaining scientifically sound data as fast as possible, with few subjects and low costs, aiming at the most effective and safe treatments[9]. While randomized controlled trials aim to verify exactly how effective a given treatment is in a prespecified and precisely defined population, during a pandemic, there is an urgent need to quickly verify a treatment that is effective at all.

Adaptive and pragmatic clinical trials search for a balance between the needs of clinicians to save lives and the needs of the medical and scientific community to reach evidence of sufficient quality and scientific rigor. Pragmatic and adaptive trials designs produce true "experimental evidence", based on a methodology of pragmatism and adaptation. Pragmatism means that physicians continue to cure their patients without the restricted limitations of protocols, obtaining a rapid recruitment of a broad population without a precise standard of care defined at the beginning, which is likely to change during the trial; adaptation means flexibility, considering possible change from the initial design as more data becomes available, considering the evolution of data.

A traditional trial in times of a pandemic is unethical and rigorousness means an increase in loss of lives. Adaptive and pragmatic designs can balance the rapidly changing standards of care with speed and agility.

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[7] K.M. Meagher, N.W. Cummins, A.E. Bharucha, A.D. Badley, L.L. Chlan, R.S. Wright, *COVID-19 Ethics and Research*, in *Mayo Clin Proc.*, vol. 95, no. 6, June 2020, pp. 1119-1123; W. Branch-Elliman, L. Soleymani Lehmann, W.E. Boden, R. Ferguson, P. Monach, *Pragmatic, Adaptive Clinical Trials: Is 2020 the Dawning of a New Age*?, in *Contemporary Clinical Trials Communications*, vol. 19, September 2020; K.A.O. Tikkinen, R. Malekzadeh, M. Schlegel, J. Ritanen, P. Glasziou, *COVID-19 Clinical Trials: Learning from Exceptions in the Research Chaos,* in *Nat. Med.*, vol. 26, no. 11, November 2020, pp. 1671-1672.

[8] Two examples of large, adaptive, pragmatic trials are: RECOVERY (UK) and SOLIDARITY (WHO).

[9] K. Al Naamani, S. Al Sinani, A.N. Barkun, *Medical research during the COVID-19 pandemic*, in *World J Clin Cases*, vol. 8, no. 15, 2020, pp. 3156-3163.

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Participants as patients should be correctly informed about the design of trials and their differences with the traditional trials, explaining the need for adaptation and pragmatism. Physicians/researchers should inform subjects that participation in research encompasses uncertainties due to the lack of knowledge about the cure/treatment: the absence of a standard of care should be mentioned explicitly in the informed consent and correctly explained to patients. This means that patients should gain awareness that a drug considered beneficial at the beginning of the trial, could become harmful during or at the end of the trial. It is essential that researchers realistically communicate potential benefits and risks in a clear and transparent way to patients. Whenever possible, appropriate time should be identified for communicating with the patient, considering his/her ability to understand in their emotional condition (e.g. fear, anxiety, etc.).
The duty of the physician/researcher to foster transparency and openness, means explaining from the beginning the uncertainties connected with the absence of a standard of care, not giving false hopes, helping the patient to acquire an adequate comprehension of the clinical situation with a realistic understanding of the potential benefits and risks. This is the only way to enable the patient to achieve critical awareness, empowerment and engagement, in a trusting environment. Incomplete information, even if justified in the paternalistic attitude to protect the patient from feelings of abandonment, cannot be ethically justified. Proportionality and graduality are required in providing information with a tailored adaptation to the specific emotional condition and fragility of the patient, in a case by case evaluation, paying specific attention to always verify the patient's effective understanding.

3. Off-label and compassionate use as trials: a gradual-accompanied consent

The move towards the use of off-label drugs and compassionate pharmaceuticals in pandemics has been unavoidable due to the urgency of treating patients and the lack of knowledge on the virus, including the lack of treatments and prevention[10]. The expression "compassionate use" can be traced in art. 83 of EC Regulation no. 726/2004 amended by Regulation no. 1394/2007. The latter introduces for the first time the definition of "advanced therapies", including not only gene therapy and somatic cell therapy, as well as tissue engineered products. The requests for "compassionate use" covers a range of treatments: the use of off-label drugs (outside prescription for indications, dosage and directions for use, but validated for effectiveness, safety and tolerability), the use of drugs undergoing validation (early access, in controlled conditions), and the use of drugs without validation (of which not even the absence of harmfulness is known).

[10] At the outbreak of the severe acute respiratory syndrome coronavirus epidemic in Italy, non–peer-reviewed articles and press releases of small clinical trials, coupled with the general amplification and uncritical reporting of "potential cures," led physicians to use many drugs off label with high expectations of their potential benefit: a similar use of off-label drugs has ethical implications and it is in the endless sound and effective in comparison with clinical trials (see A. ADDIS ET AL., *Promoting Better Clinical Trials and Drug Information as Public Health Interventions for the COVID-19 Emergency in Italy*, in *Annals of Internal Medicine*, vol. 173, pp. 654-655, 2020, https://www.acpjournals.org/doi/full/10.7326/M20-3775?journalCode=aim, last accessed on May 31st 2021).

There are many ethical questions emerging in this context: To what extent does a right to the freedom of treatment, a right to hope/right to try exist? When does the hope become illusion, with negative consequences on the health of the patient and for the whole society? [11]

In the first case the risks are generally sufficiently controlled, even if no guarantee of recovery may be given: at least the risks of harmfulness, even if the risks remain uncertain because of the lack of knowledge of the virus. In the second case the risk margin and uncertainty increase, as the clinical trial process of the pharmaceuticals has not been concluded. The latter is the most problematic case since no data exist even on the harmfulness of the drug. In times of pandemics, the danger of contagion and the rapid spread of the pandemic, with high levels of mortality, underline the urgency to try and find a solution, not only in the interest of the single individual but also of the community[12]. In this case the risk and uncertainty for the individual must be balanced against the benefit for the whole society as well as for the single person.

In the case of Covid-19, the legitimacy of access to compassionate use depends on the urgency and emergency in life threatening cases, with no therapeutic alternatives available[13].

The ethical evaluation is given by a committee of experts, designated by public healthcare facilities (and centralized during pandemics, in some countries), in conditions of transparency, absence of conflicts of interest, publication both of the composition of the products and the results of the treatment, exhaustive explanation given to the patients on the potential dangerousness of non-validated treatments, responsibility for the drugs borne by the manufacturers and monitoring carried out by national healthcare bodies. Only under these conditions can "compassionate" treatments be considered ethically licit and be included in the general right to health.

The access to unproven therapies should not be a "hidden" or "fake" trial, which, by means of the compassionate use, obtains results by bypassing the usual long trial procedures and authorization. Furthermore, the access to treatments should not be coercive to the extent that, owing to pandemics, there is a danger to public health. The right to treatment should always be balanced with the economic sustainability of healthcare and with medical accountability (insofar as it is the doctor that prescribes and administers the drug). Consent must be suitably informed, covering the uncertainties, the limits to hope and possible harmfulness or even lethalness. Risk-taking should always be personal, not substitutable and conscious.

The doctor should be recognized as having the possibility to abstain from prescribing drugs or technologies for compassionate use, insofar as, to the best of his knowledge and his own conscience, he considers them dangerous treatments and too risky for the patient (a sort of "experimental obstinacy"). The right to autonomy and professional deontological responsibility prevails over the possible need to guarantee the right to hope and to try of the patients (right of

[11] See art. 37 of the *Declaration of Helsinki* (updated in October 2013) that provides for the possibility of "unproven interventions in clinical practice".

[12] 'Expanded access' refers to treatment offered to patients in the absence of other effective treatment options, an individual and public health emergency.

[13] THE ITALIAN COMMITTEE FOR BIOETHICS has extensively addressed this issue in the Opinion "Biomedical research for novel therapeutic treatments within the Covid-19 Pandemic: ethical issues", October 22nd, 2020, http://bioetica.governo.it/en/opinions/opinions-responses/biomedical-research-for-novel-therapeutic-treatments-within-the-covid-19-pandemic-ethical-issues/ (last accessed June 9th, 2021).

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self-determination of the patient), that can also be a result of a sort of social pressure to try. This is not a case of conscientious objection, since the physician does not find himself faced with a conflict of values or different views on life, rather it is a case of “scientific objection” respecting those fundamental principles that are at the basis of medical practice, that is the protection of patient safety.

It follows that there is an obligation for the doctor to provide comprehensive, clear and comprehensible information adopting an empathic attitude. The shared purpose (of both physicians and patients) is to allow the patient to make an informed decision appropriate to the situation with proportionate and realistic expectations. Maximum transparency and clarity is required of the doctor especially if the possible side effects and potential harmful effects of the therapy are not known, so as to allow the patient to exercise their autonomy.

Informed consent, even with all the limits due to the specificity of the situation, can in part only be a declaration of personal risk assumption, considered valid only if expressed following a discussion with doctors who share and explain the reasonableness of the request. The absence of validated therapies cannot legitimize consent to a presumed treatment devoid of any rational justification and based only on the patient's will. Otherwise there is the risk of transforming patients from victims into guinea pigs to be exploited, also for the indirect benefit of society. It is easy to move from compassion to illusion, endorsing practices that have no justification on bioethical basis.

The dramatic situation could result in a condition of mutual pressure between patient and doctor: one expects a remedy at any cost and the other tends to provide it in every way. Divided between resignation that is difficult to accept and compassion that is difficult to achieve, the doctor has a duty to recommend the best “available” therapy, but in the absence of known cures the concept of "availability" becomes vague, it extends to the probable and the possible. The proportionality of the information should lie in the difficult relationship between the maximum expected benefit and the least foreseeable harm. If the doctor cannot become a “seller of illusions” that supports any request, he cannot ignore, in the paramount interest of the patient's health, those innovative therapeutic perspectives that appear plausible to his professional conscience. Patients who want to have access to a "compassionate" therapy must be guaranteed comprehensive explanations on the potential danger of this type of treatment. The patient must also be informed that the treatment will be administered according to the indications and methods approved by the ethics committee and the panel of experts.

4. Possible alternatives: re-consent

Informed consent for clinical research also requires information on relevant alternatives that might be beneficial to the individual.

In the context of Covid-19, where there are no standard of care and approved treatments, the relevant alternatives may include only “supportive care”, or also the “off-label use” of other available therapies and “compassionate use”. It is a responsibility of the physician to properly inform the patient on possible alternative clinical trials, if it is a good option for patients. Clinicians may also be

asked to make recommendations between multiple clinical trials, given the proliferation of COVID-19 studies.

The process of re-consent can be identified as an action in which a subject (or representative) makes a decision about whether to re-affirm a previous choice of clinical trial to participate in research. Re-consent should inform about new, potentially beneficial findings that have emerged since the initial consent. In this sense consent needs to be dynamic, as a process and continuously updated, keeping pace with the speed of new developments.

A need to re-consent may involve a newly approved therapy for Covid-19 (hence, an alternative to participation), new information on therapy offered in the trial that was discovered during prior treatment of subjects. With rapid changes in understanding of the disease, and hundreds of weekly publications focused on the topic, it may also be unclear how often such disclosure and re-consent should take place. This challenge may be further magnified by rapidly expanding opportunities for access to products.

5. Deferred consent as exception for informed consent and the role of Ethics Committee

Some Covid-19 trials allow the inclusion of patients in their protocols on the basis of the so-called "deferred consent" or "exemption from informed consent", used in emergency-care research settings[14], when patients are not capable to giving consent and legally authorized representatives for critically ill patients are unable to provide consent or cannot be contacted in time due to infection control policy in place and the urgency[15]. Consent for continuation of trial enrollment and data collection is obtained only when the patient is capable of providing informed consent or the representative is available.

The ethical conditions of "deferred consent"[16] are: the research participant needs immediate treatment; the participant is incapable of giving informed consent; an attempt has been made to obtain informed consent from the participant's legal representative; the study cannot be conducted in a population that has not developed the condition under study; informed consent to remain in the study is obtained from the participant or the legal representative as soon as possible; the treatment under investigation is considered to be potentially beneficial for the participant; the research

[14] For example, the RECOVERY protocol, in which patients are randomly assigned to various treatment arms (among others, dexamethasone), states "Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomisation and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity" (RECOVERY Trial Protocol, par. 2.2, https://www.recoverytrial.net/files/recovery-protocol-v7-0-2020-06-18.pdf, last accessed May 31st 2021).

[15] R. VAN DER GRAAF, M.-A. HOOGERWERF, M. C. DE VRIES, *The Ethics of Deferred Consent in Times of Pandemics,* in *Nature Medicine*, vol. 26, 2020, pp. 1328–1330.

[16] THE ITALIAN COMMITTEE FOR BIOETHICS dealt with this issue in the 2012 Opinion "Clinical trials in adult or minor patients who are unable to give informed consent in emergency situations", http://bioetica.governo.it/en/opinions/opinions-responses/clinical-trials-in-adult-or-minor-patients-who-are-unable-to-give-informed-consent-in-emergency-situations/ (last accessed May 31st 2021).

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participant has not objected in advance to research participation; the research cannot be conducted without the option of deferred consent; the risks of receiving the intervention are minimal, at least in comparison with the absence of treatment, having no alternatives; the research ethics committee has approved the deferred-consent procedure; the possible use of advance directives before participants become incapable of giving informed consent.

In the context of Covid-19, respiratory distress is the prime symptom of Covid-19, and the condition of a patient may deteriorate suddenly. In the intensive care unit, the treatment of patients with Covid-19 consists mainly of ventilator support. Additional experimental anti-viral or anti-inflammatory medications may be added to this "standard treatment": in many settings, additional medications are provided mainly within the context of clinical trials. In the case of Covid-19, patients may be intubated, which makes it impossible for them to provide consent. The contacting of the legal representative might not be immediately available because they may not be allowed in the intensive care unit because of lack of protective equipment, because they are in self isolation or because travel is not recommended. If the legal representative cannot be physically present, remote informed consent is an alternative but can be logistically difficult, and may cause delays. Several protocols have included deferred-consent procedures. If there is a "therapeutic window", patients can sign an informed-consent document preemptively, for inclusion at a later time when their condition deteriorates and authorization is no longer possible, as an advance directive.

Ethics Committee can authorize research without requiring informed consent from participants if (1) the research would not be feasible or practicable to carry out without the waiver; and (2) the research has important social value; and (3) the research poses no more than minimal risks to participants and there are no previously expressed objections by the patients. The Ethics Committee should carefully review justification for inclusion of vulnerable participants, thoroughly assess risk–benefit and risk minimization, and thoroughly scrutinize the recruitment process, informed consent document, educational material for participants, and clinical trial agreement/insurance policy, prior to approval of the clinical trial. The Committee should monitor the conduct of trials through review of periodic study progress reports from the investigators, review audiovisual recording and written documentation of the informed consent process in real time when the patients are enrolled to ensure that the consent process is voluntary and valid in the vulnerable population, and the conduct of clinical trials is in compliance with the approval.

6. Tele-medicine and remote information-monitoring: an electronic-digital consent

Covid-19 poses many unique challenges to the implementation of clinical research, particularly in relation to the processes of informed consent. Traditional methods were no longer plausible and possible, because face-to-face discussions may expose researchers and patients to increased risk of infection[17]. The research personnel obtaining consent were considered non-essential workers, not

[17] Due to COVID-19 isolation measures or safety, electronic informed consent should be considered. If not possible electronically, a call phone or video communication with the investigator, patient, and an impartial witness have been suggested. If the signed consent form cannot be collected from the patient, an attested copy by the witness and investigator who participated in the call should suffice. The details of the above procedure should be included with the informed consent in the source notes for records.

receiving priority for personal protective equipment in light of national shortages. And due to hospitals restricted visitor access, legally authorized representatives were no longer present. In response to these challenges, and to facilitate the process, an electronic consent (e-Consent) should be implemented. It is necessary to reflect on the modality of electronic informed consent.

The two main goals of eConsent are the same as traditional informed consent: first to conduct a comprehensive dialogue with the patient regarding study procedures so that they can make an informed decision about participation fully aware of the risks and benefits involved and, second, to document this conversation and discussion appropriately. With eConsent, both of these goals can be achieved using a secure digital platform on an electronic device, eliminating the use of paper forms[18].

There are many potential benefits of eConsent.

It allows for enhanced infection prevention and control (consent may take place over video chat or phone, decreasing research staff exposure to virus, and decreasing research-related use of personal protective equipment); potential research participants can utilize Internet-connected device to virtually discuss the trial with researchers and access the informed consent document. This presents an advantage over paper consent forms, where the transmission of Covid-19 via paper still remains uncertain. The same procedures could be used to facilitate a consent discussion with a critically ill patient who is not physically present in the hospital. eConsent also expands participations to populations traditionally not afforded clinical research opportunities through "remote enrollment" (recruitment in rural hospitals, recruitment of patients in multiple hospitals, remote eligible patient); enhanced understanding, as digital consent often makes use of boxes, flexible text size, multimedia incorporated tools that increase readability, engagement and retention by ensuring critical information available online; enhanced transparency process and traceability, verification of regulatory compliance (paper consent forms often have missing signatures or incorrect dates or times; warnings about missing items, ensure that the most updated version of a consent form is used).

But there are many challenges. Because of the use of digital technologies, it may reduce equitable access to clinical trials across the socioeconomic spectrum (the lack of smart devices and technological illiteracy). While eConsent provides benefits to the informed consent process, investigators must consider and plan for the associated challenges to ensure potential participants have an equitable opportunity to participate in research. This should be clear in the information process. Patient hesitancy should be understood and accommodated for by researchers.

The implementation of these alternative procedures (telephone contacts, followed by confirmation e-mails or validated electronic systems) does not exempt from obtaining written consent as soon as the situation permits, on the first occasion in which the subject appears at the site.

In the case of temporary verbal consent, the presence of an impartial witness who certifies the successful administration of the consent and affixes the date and signature on the informed consent

[18] With the outbreak of COVID-19, the FDA released additional documents recommending eConsent over traditional consent, when appropriate technology is available (see FDA, *Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*, March 2020, https://www.fda.gov/media/136238/download, last accessed May 31st 2021).

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document is required. It is up to the investigator to certify the method of selection of the impartial witness, who should be external to the research teams.

7. Restrictions and changes of protocols: informed consent and additional risks

The main challenges emerging during the Coronavirus pandemic in clinical trials also on non-Covid-19 pathologies are mainly due to the results from restrictions at health care facilities and changes in availability of researchers/personnel. Some trial participants or investigators might also be required to self-isolate because of the infection or because of shortage of protective equipment for researchers and participants. In specific circumstances it may cause a moral dilemma in keeping trials running because of the increase of the risks, which need to be clarified to patients, in addition to the informed consent for research. In this sense, the spread of the virus required/is requiring further amendments to protocols: the addition of these risks are required as mandatory. All these factors have an impact on the recruitment, assessment, and provision of clinical trials (for non Covid patients)[19].

The impact of Coronavirus pandemic needs to be considered both on ongoing trials and on new clinical trials. Sponsors must consider the restrictive measures imposed (varying in different countries) including limitations of trial participants and staff confinements and their ability to visit, interview and notify adverse effects. Participants should be informed regarding the impact the situation might have on the trial protocol, with possible changes in the risk/benefit balance and possible interruption of trials. Regulatory bodies have stopped or delayed approvals for non-Covid-19 new trial registration: and also this information needs to be given to patients. At any stage, it is very important for participants to be kept informed of changes to study and other plans that could impact their care.

Since trial participants may not be able to visit the site for the specific protocol visits and investigations, sponsors should evaluate if alternative measures such as virtual visits, alternative locations for assessment, including imaging centres and labs, could suffice, only after ensuring the safety of the participant. This is important for trials which include those who need additional safety monitoring.

8. Clinical trials and patient's vulnerabilities

The Covid patient is a particularly vulnerable patient: because he is sick, because the disease has no cure, because he is in isolation with the lack of contact with his family or friends, and because of the safety conditions in which the health staff must work, that is, with protective devices that can also make personal recognition and relationships difficult. It should also be considered that in the most emergency phases of a pandemic, health workers can be so overwhelmed by events that they have difficulty or are unable to relate to patients beyond providing strictly therapeutic interventions and

[19] A.G. SINGH, P. CHATURVEDI, *Clinical trials during COVID-19*, in *Head & Neck*, 2020, pp. 1–3; E. BAGIELLA, D.L. BHATT, M. GAUDINO, *The Consequences of the COVID-19 Pandemic on non-COVID-19 Clinical Trials,* in *J. Am. Coll. Cardiol.*, vol. 76, 2020, pp. 342-345.

treatments, often life-saving measures. It is therefore necessary to outline procedures that, on the one hand, meet the needs of healthcare personnel and patients who are faced with the emergency and, on the other, guarantee the ethical standards of research and patient protection.
The emphasis on the autonomy of patients should take into account the specific vulnerability of Covid-19 patients, experiencing diminished capacity, due to the nature of the symptoms and need for mechanical ventilation and sedation. In addition, the stress of being sick triggers anxiety, and further clouds decision making. Patients frequently make their decisions on participation in trials based on the way information is presented to them verbally, rather than reading a written consent form, and clinicians' time constraints during the pandemic may limit the ability to sufficiently provide this need for patients, further compromising their informed consent. The quality of the informed consent process may be less than optimal.
Covid-19 patients in moderate to severe clinical condition should be considered particularly vulnerable. While full autonomy should be pursued for all patients, early deliberation on the consent process, before any deterioration is notable, should take place. Stressors associated with the pandemic, including social distancing and the likelihood of debilitating symptoms, should be considered. Efforts should be made to conduct a consent process with family members, using advance video technology for those who cannot attend the clinical space. Whenever possible, obtaining consent should be done after limiting unsettling pressures (noise, distracting commotion).

9. Specific vulnerabilities: age, gender, ethnicity

Minors

Minors have been less affected by Covid-19, and when infected become less seriously ill, so that the need for trials was not so urgent as in the adult population. However, some children did develop severe disease. So completely excluding these vulnerable populations from clinical trials, could exclude them from therapies. The risk/benefit calculations of therapies derived from adult trials cannot be readily extrapolated to children. Gaps in our knowledge of pediatric Covid-19 further complicate assessments of risk and benefit. Combined pediatric–adult trials may be a strategy to gather drug efficacy data in children, but it is not clear if these existing trials will have sufficient relevance to analyze efficacy in children specifically[20].
Multicentre coordinated trials should be prioritized. These would support sufficiently powered studies to test therapies for sicker, hospitalized children and facilitate analyses among subgroups with specific predisposing conditions. Existing trial networks like the Pediatric Trial Network could be enlisted. Some therapeutics trials in adults could be extended to include children, as a small number of studies are already doing. Joint studies also would enable resource sharing, alleviating pragmatic barriers to pediatric trials. Children receiving drugs for Covid-19 should at least be offered the opportunity to participate in prospective observational studies. Although these studies are limited in their ability to establish efficacy, they would allow prospective data collection on clinical and virological and drug-associated adverse effects. It would also permit comparative subgroup analyses

[20] T.J. HWANG, A.G. RANDOLPH, F.T. BOURGEOIS, *Inclusion of Children in Clinical Trials of Treatments for Coronavirus Disease 2019 (COVID-19)*, in *JAMA Pediatr*, vol. 174, no. 9, 2020, pp. 825-826.

between groups of children with varying risks for adverse outcomes. Conducting controlled, coordinated pediatric trials is the only way to learn whether the potential benefits of these drugs outweigh their risks.

The exclusion of children from Covid-19 clinical trials is a lost opportunity to generate knowledge to guide the treatment of pediatric populations. Without adequate studies, clinicians would need to prescribe approved pharmaceuticals for children off label. Simple extrapolation from adult to pediatric patients may not account for developmental differences in pathophysiology and drug metabolism. In the absence of pediatric data available at the time of regulatory approval, children may be exposed to possibly unsafe and ineffective treatments. Early reports were that the clinical course of Covid-19 generally appears to be milder in children, but there are emerging epidemiologic data suggesting that the infection can be serious in certain pediatric populations, underscoring the public health need for rigorous study of potential Covid-19 therapies in children. And informed consent obtained from parents, and informed assent from children, according to their age and maturity.

Elderly people

Older adults[21] face increased risk of morbidity and mortality due to Covid-19, and so ongoing clinical trials that enroll geriatric participants have been disrupted, appropriately so, in light of these increased risks. Older adults are substantially under-represented in clinical trial research, and this situation may worsen this discrepancy. Scientists in ageing appreciate the necessity of older adults' inclusion within clinical trials, but the vulnerability to increased exclusion in clinical trials of this population is high, and this is particularly evident in pandemics. Attention to clinical trial development with special attention to the need for inclusion of older adults and precautions is greatly required to sustain current efforts, at a minimum, and ideally, enhance recognition of the value of including older adults in clinical trial research.

The effects of Covid-19 on geriatric clinical trial research will be long-lasting. Trials that involve in-person cognitive assessment face challenges as they move to other modalities for testing, which may influence results. Exclusion criteria that could limit participation of elderly adults such as comorbidities, cognitive impairment, limitation of life expectancy; and the assessment of long-term outcomes such as the need for rehabilitation or institutionalization. Elderly persons are under-represented and demonstrate that no trial has specifically addressed them. There are understandable and sound reasons for the exclusion of elderly patients from some trials, particularly those designed for the early development of novel therapeutics. There is often limited experience in elderly populations with the drug. These patients have an increased risk of drug-drug interactions due to potential polypharmacy and age-related physiological changes affecting pharmacokinetics and pharmacodynamics. When drugs of interest are being given off-label to elderly patients essentially *en*

[21] E.K. RHODUS, S.H. BARDACH, E.L. ABNER, A. GIBSON, G.A. JICHA, *COVID-19 and Geriatric Clinical Trials Research*, "Aging Clinical and Experimental Research", 2020, volume 32: 2169–2172(2020); V. PRENDKI, N. TAU, T. AVNI, *A Systematic Review Assessing the Under-representation of Elderly Adults in COVID-19 Trials*, in *BMC Geriatr*, 20, 538 (2020).

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masse, trial protocols should adapt to reflect the larger clinical reality around them, allowing for increased and more equitable representation of this population.

The under-representation of the elderly in Covid-19 trials is an acute manifestation of a larger problem: the elderly tend to be disproportionately excluded from trials in all domains. Elderly patients with cognitive, psychiatric or physical comorbidities are largely absent from, leaving clinicians to rely on data from inferior studies such as retrospective case, which may be unreliable due to confounding by indication and other biases. As the aging population continues to grow in size, medical research must better reflect this growing segment of the population. This is especially true regarding Covid-19, which is more common and more severe in the elderly, causing devastating effects.

Ethical standards should facilitate the inclusion of elderly adults with more adapted informed consent, including the possibility to obtain consent by proxy if the patient has diminished capacity. Clinical research including the elderly has never been easy; nevertheless, future trials will need to address this vulnerable and oft-forgotten population, particularly when these individuals are regularly receiving off-label therapies anyway.

Women, pregnant and breastfeeding women

Pregnant and breastfeeding women are excluded from participating in clinical trials during this pandemic[22]. This "protection by exclusion" of pregnant women from drug development and clinical therapeutic trials, even during pandemics, is not unprecedented[23]. This is another missed opportunity to obtain pregnancy-specific safety and efficacy results, because therapeutics verified for men and non-pregnant women may not be generalizable to pregnant women, because of their specific condition. Without clear justification for exclusion, pregnant women should be given the opportunity to be included in clinical trials for Covid-19 based on the concepts of justice, equity, autonomy, and informed consent. Even during the Ebola virus epidemic, pregnant women were excluded from all therapeutic and vaccine-development trials. This automatic disqualification denies pregnant women the potential for benefit given to other patients[24].

[22] M.M. CONSTANTINE, M.B. LANDON, G.R. SAADE, *Another Missed Opportunity to Include Pregnant Women in Research During the Coronavirus Disease 2019 (COVID-19) Pandemic,* in *Obstet Gynecol*., vol. 136, no. 1, July 2020, pp. 26-28.

[23] For decades, pregnant and breastfeeding women, and in general fertile women, have been excluded in consideration of the risks for the foetus or for the newborn. The recommendation about their inclusion, always safeguarding also the foetus/the newborn interests, have been one of the new elements in the revised CIOMS Guidelines (2016): the 2002 CIOMS guidelines on research with pregnant women underwent major revisions to strengthen the specific protection mechanisms of women interests and rights), such as the conditions under which risks in research with pregnant women are acceptable (see J.J. VAN DELDEN, R. VAN DER GRAAF, *Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans, Journal of the American Medical Association*, vol. 317, no. 2, 2017, pp. 135-136).

[24] Since the 1950s, and after the discovery of the association between exposure to certain drugs during gestation and birth defects, pregnant and breastfeeding women have been systematically excluded from drug-development and clinical trials. Despite several policy and legislative changes, including the National Institutes of Health Revitalization Act of 1993, the U.S. Food and Drug Administration's guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, the National Institutes of Health's guidance for the inclusion of women in clinical trials, the establishment of the Office on Women's Health, and the estab-

Results from studies without pregnant women cannot be automatically extrapolated to a pregnant population. This lack of generalizability is due to the physiologic changes in pregnancy, which affect the pharmacokinetic and pharmacodynamic of drugs. The lack of data specific to pregnancy will negatively affect the health of pregnant women and their access to interventions in the current and next outbreak. This will create a knowledge gap concerning the safety and efficacy of any drugs or interventions that may emerge from current Covid-19 research. Although fetal safety is the most cited reason for the exclusion from research studies of pregnant women and those who could become pregnant, it is unethical to automatically preclude them from carefully designed clinical therapeutic research studies.[6]

The perception that pregnant or breastfeeding women are a "particularly vulnerable population" needing protection from exploitation research studies has hindered progression of treatment and care. Pandemics are outlining a cultural shift within the research community to view this population as in need of more evidence, particularly in pharmaceutical research. Pregnant women should be permitted to determine their eligibility and entry into a research study based on the principle of informed consent.[6]

Although one must consider the safety of a drug in pregnancy, it is equally important to consider the risks of not treating or inadequately treating pregnant women. Similarly, the risk to the fetus of treatment needs to be weighed against the risk of inadequate treatment, given that many of the conditions that affect the mother will ultimately adversely affect the fetus if not treated. Rather than automatically excluding them, investigators should consult with experts in obstetrics, and obstetric pharmacology. Specific trials involving pregnant woman are needed in order to have safe and effective treatments for them. At the moment, evidence is largely confined to observational studies and use of off-label pharmaceuticals; there remain few systematic studies on the condition of pregnant women and no inclusion of pregnant women in trials of the general population. The trials should be clearly accompanied with information on potential benefits and risks, both for the woman and the foetus.

Ethnicity

Data on ethnicity in patients with Covid-19 in the published literature remains limited[25]. The reasons for under-representation of ethnical groups in research are complex and could be attributable to hesitancy on the part of participants, lack of inclusion by researchers, and other socioeconomic factors and structural inequalities. Barriers to participation in research include language difficulties, low research awareness, health illiteracy or mistrust of research, stigma, cultural values and beliefs about research, poor engagement from researchers, and general inaccessibility to research in deprived areas, including concerns of costs of time and money, and discrimination.

lishment of the Task Force for Research Specific to Pregnant and Lactating Women, pregnant women remain 'therapeutic orphans', with the vast majority of current accepted therapies for medical conditions never having been studied in pregnancy. THE ITALIAN COMMITTEE FOR BIOETHICS has explored this issue in the opinion *Pharmacological trials on women,* November 28th, 2008, *http://bioetica.governo.it/en/opinions/opinions-responses/pharmacological-trials-on-women/* (last accessed June 9th, 2021).

[25] D. PAN ET AL., *The impact of ethnicity on clinical outcomes in COVID-19: A systematic review*, in *EClinicalMedicine*, 23, 2020, https://doi.org/10.1016/j.eclinm.2020.10040 (last accessed June 9th, 2021).

Recruitment strategies and information provision approaches that work for the majority population may be ineffective for ethnical groups. Interpreters, translators and cultural mediators could be needed, along with culturally sensitive recruitment methods. Ensuring research is culturally and linguistically accessible and inclusive requires the commitment and resources of researchers from the start. The Covid-19 pandemic has exposed a problem that has been known for a long time. Results from Covid-19 research must apply to everyone in the community who will be a candidate for treatment or prevention, and also ethnical groups or minorities should be an integral part of that effort. If research fails to engage all those who could benefit, there is no guarantee that the results will apply to populations not included in the research. Thinking about participants' ethnicities when designing and reporting research needs to become as routine as thinking about their age and gender. Researchers, research funders, and public health and policy agencies all have a duty to ensure that concerted action is taken for research studies to serve and represent the whole community, not just part of it, above all in the Covid-19 pandemics.

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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.

Special issue

Ethical and regulatory issues in vaccine research in the pandemic context and in the case of human challenge studies: implications for informed consent

Margherita Daverio*

ABSTRACT: In the pandemic context several specificities should be underlined for the case of vaccine trials, in addition to all ethical concerns raised for research related to pharmacological treatments which are also valid for vaccine research. Study population in vaccine trials is built up with healthy volunteers that should be carefully and fairly selected; as far as vaccine for emergency use are approved, the use of placebo in controlled studies raises ethical questions that should be discussed. Participants in vaccine trials should in any case be unduly influenced by any form of payment, and the gratuity of their act should be stressed in the communication and consent process. Moreover, in the context of experimentation with vaccines, sensitive ethical issues can arise also from the so-called "challenge studies", since they concern intentionally infecting healthy people to investigate diseases and their treatments (human challenge trials involve exposing healthy volunteers to a pathogen to learn more about the disease it causes and to test vaccines quickly). The contribution finally includes a specific list of aspects to be included in well-designed information and consent process for participants' in vaccine research in the Covid-19 pandemic.

KEYWORDS: Ethics of vaccine research, human challenge studies, informed consent, healthy volunteers, placebo

SUMMARY: 1. A brief overview of ethical and regulatory issues in vaccine research in the pandemic context – 2. Ethical issues in vaccine research in the pandemic context: implications for informed consent – 2.1 Vaccine safety, including risk and potential benefits assessment for participants. 2.2 Issues related to the involvement of healthy volunteers, including a fair selection of study participants – 2.3 The use of a placebo – 2.4 The gratuity of the act of participants in the study – 3. Regulatory issues in vaccine research in the pandemic context: implications for informed consent – 4. The case of human challenge studies for vaccine against Covid-19: ethical issues and implications for informed consent – 5. Conclusion: key aspects of the informed consent process in vaccine research in the pandemic context.

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1. A brief overview of ethical and regulatory issues in vaccine research in the pandemic context

Research and development of vaccines against Covid-19 has a high common good impact[1], representing the major contribution in facing (and possibly stopping) the pandemic. To date, WHO has so far validated for emergency use the Pfizer vaccine, the Johnson & Johnson vaccine, the Moderna vaccine and AstraZeneca vaccine. WHO's Strategic Advisory Group of Experts on Immunization (SAGE) has also found these vaccines to be safe and effective and made recommendations on their use. The WHO constantly documents vaccine candidates development and particularly those in clinical development[2].

Generally very safe and effective, vaccines are also an efficient way of preventing disease[3]. In the past, vaccines have been always developed through a series of steps that could take many years[4]. In the current context, given the urgent need for Covid-19 vaccines, unprecedented financial investments, scientific collaborations, and regulatory efforts have contributed to accelerate the processes related to vaccine research, in order to save as many lives as possible. Clinical trials in human medicines, including those for Covid-19 vaccines, are authorised and managed at national level in the EU. National competent authorities and ethics committees ensure that studies are scientifically sound and conducted in an ethical manner. Human pharmacology studies (phase I trials) generally involve between 20 and 100 healthy volunteers to confirm if the medicine behaves as expected based on laboratory tests. This can establish: if the vaccine triggers the expected immune response; if the vaccine is safe to move into larger studies; which doses can be adequate. Phase II trials involve several hundred volunteers. The purpose of this phase is to study the best doses to use, the most common side effects and how many doses are needed. These studies also check that the vaccine triggers a good immune response in a broader population. In certain cases, it could also provide some preliminary indications of how well the vaccine will work (efficacy). Clinical efficacy and safety studies (phase III trials) include thousands of volunteers. This phase shows how efficacious the vaccine is at protecting against the infection compared with placebo (dummy) or alternative treatment and what are the less common side effects in those receiving the investigational vaccine[5]. In Phase IV trials, surveillance of adverse effects or any medicine-related problem continues also after the marketing authorization.

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[1] UNESCO International Bioethics Committee (IBC) and the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), *UNESCO's Ethics Commissions' Call for Global Vaccines Equity and Solidarity. Joint Statement*, February 24th 2021, §3, https://unesdoc.unesco.org/ark:/48223/pf0000375608; Italian Committee for Bioethics, *Vaccines and COVID-19 : ethical aspects on research, cost and distribution*, Opinion, November 27th 2020, http://bioetica.governo.it/en/opinions/opinions-responses/vaccines-and-covid-19-ethical-aspects-on-research-cost-and-distribution/ (last accessed April 15th 2021).

[2] See https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines (last accessed June 14th 2021).

[3] C. Grady, *The ethics of vaccine research*, in *Nature Immunology*, vol. 5, no. 5 (May 2004), pp. 465-468, p. 465.

[4] S. Hanney et al., *From COVID-19 research to vaccine application: why might it take 17 months not 17 years and what are the wider lessons?*, in *Health Research Policy and Systems* (2020), 18:61; P. H. Kamble et al., *Expedited COVID-19 vaccine trials: a rat-race with challenges and ethical issues*, in *Pan African Medical Journal*, vol. 36, no. 206, 2020.

[5] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring (last accessed May 31st 2021).

On an ethical level, vaccine research in general shares all the ethical issues of clinical research involving humans[6] and particularly those of translational clinical research, which deals with first-in-human trials[7].

There are some ethics issues which are specifically related to vaccine research[8]. Thus, in the pandemic context several specificities should be underlined for the case of vaccine trials, in addition to all ethical concerns raised for research related to pharmacological treatments[9] which as mentioned are also valid for vaccine research. Vaccine trials in fact fall within interventional research and they are not "low interventional studies" with minimal risk. Vaccine trials are non-therapeutic trials, where the scope of research is not aimed at identifying a treatment or a cure, but it is oriented to assess and verify safety and efficacy of a vaccine; for this reason, study population in vaccine trials is built up with healthy volunteers that should be carefully and fairly selected. As far as vaccine for emergency use are approved, the use of placebo in controlled studies raises ethical questions that should be discussed. Participants in vaccine trials should in any case be unduly influenced by any form of payment, and the gratuity of their act should be stressed in the communication and consent process.

On the regulatory level, as mentioned above, a rigorous procedure ensures quality, efficacy and safety and this is why vaccine trials usually take not less than 10 years to be developed. In the pandemic context, however, there have been regulatory efforts on a global level in order to accelerate as much as possible vaccine emergency approval, always basing on sound scientific data and taking into primary account the protection of human subjects involved. Vaccine development for Covid-19 vaccines is being fast-tracked globally. Early scientific advice from regulators helps speed up development[10]. So called "regulatory flexibility"[11] has been adopted by ethics and regulatory bodies on global and regional levels in order to accelerate as much as possible the experimental process for treatments and vaccines against Covid-19, always safeguarding scientific and ethical requirements of study protocols. Within the European Union the European Medicines Agency (EMA) adopted a governance of vaccine research

[6] See COUNCIL OF INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCE (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, Council of International Organizations of Medical Science (CIOMS), Geneva, 2016, https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf (last accessed May 31st 2021).

[7] See C. PETRINI, L. MINGHETTI, S. BRUSAFERRO, *A few ethical issues in translational research for medicinal products discovery and development*, Annali dell'Istituto Superiore di Sanità, vol. 56, no. 4, 2020, pp. 487-491.

[8] For the specificities of the ethics of vaccine research, see also C. GRADY, *The ethics of vaccine research*, cit.

[9] On the implications of these issues for informed consent, see L. PALAZZANI, *Informed consent in clinical trials in the context of the pandemic between bioethics and biolaw: a general overview*, in *BioLaw Journal-Rivista di Bio-Diritto,* Special Issue no. 2/2021, pp. 3-15; L. PALAZZANI, *Clinical trials in the time of a pandemic: implications for informed consent* in *BioLaw Journal-Rivista di BioDiritto,* Special Issue no. 2/2021, pp. 39-50.

[10] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring (last accessed June 9th, 2021).

[11] "Regulatory flexibility" aims at guaranteeing the achievement of all these requirements, while accelerating as much as possible the process for scientific and ethical evaluation of clinical protocols concerning treatments for and vaccines against COVID-19. This has been instituted at international and national level, for example establishing scientific, regulatory and ethical bodies with the specific task of evaluating clinical studies related to COVID-19 respectively at a scientific and ethical level. See also H. FERNANDEZ LYNCH ET AL., *Regulatory flexibility for COVID-19 research*, in *Journal of Law and the Biosciences*, Jan-Jun 2020; 7(1), 1–10.

based precisely on regulatory flexibility; EMA offers informal consultation with its Covid-19 Task Force (ETF) and rapid scientific advice. In par. 3 we will recall main regulatory issues related with vaccine research in the pandemic contexts, with reference to informed consent.
An important point raised up in the pandemic context is the issue related to human challenge studies, i.e. the possibility of deliberately infecting healthy volunteers in order to speed up vaccine testing. Even considering many positive aspects of this kind of trials, human challenge studies raises sensitive ethical issues, mainly regarding participants' safety and risks exposure. In 2020 the WHO issued a document on this issue[12] and on human challenge studies (or controlled human infection) a large debate raised also in scientific literature.

2. Ethical issues in vaccine research in the pandemic context: implications for informed consent

In the context of a moral constitutive pluralism in the bioethical debate that continues to raise theoretical discussions and different practical interpretations[13], the reflection on the experimentation on human beings has reached some common guidelines at bioethical and biolegal level, making it possible to configure an international and national normative framework of reference. As in clinical research in general, the informed consent process is essential for the potential participant to be informed of the fundamental elements of the research protocol, of the possible benefits but also of the risks and of the level of uncertainty relating to the research project, in order to be able to choose freely and consciously[14]. Ethical[15] and legal[16] requirements are clear in recommending and regulating an adequate informed consent process as a key element of clinical research, in order to protect human subjects involved as participants. In the disclosure of the information, therapeutic misconception[17] or unrealistic optimism of the participant should be taken into account, as they are factors that can

[12] WHO, *Key Criteria for the Ethical Acceptability of COVID-19 Human Challenge Studies*, 6 May 2020, https://www.who.int/publications/i/item/WHO-2019-nCoV-Ethics_criteria-2020.1 (last accessed May 31st 2021).
[13] For a reconstruction of the different theories in bioethics and different biolaw models, see L. PALAZZANI, *Bioethics and Biolaw: Theories and Questions*, Giappichelli, Torino 2018, pp. 176.
[14] WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki. Ethical principles for medical research involving human subjects*, 1964 (last revision 2013), https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last accessed April 15th 2021). The issue of consent is widely explored in the bioethical literature: for a general overview, see P. MALLIA, *Consent: Informed*, in TEN HAVE H. (ed) *Encyclopedia of Global Bioethics*, Springer, Cham, 2016, https://doi.org/10.1007/978-3-319-09483-0_120; in addition also, R. R. FADEN, T. L. BEAUCHAMP, *A history and theory of informed consent*, Oxford University Press, New York, 1986.
[15] COUNCIL OF INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCE (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, cit.
[16] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=IT, (last accessed April 15th 2021).
[17] P. APPELBAUM ET AL., *Therapeutic misconception in clinical research: frequency and risk factors*, in IRB, vol. 26, 2004, pp. 1–8.

prevent the subject from understanding correctly the risks that a clinical study can imply[18]. According to the principles of biomedical ethics, a clear and complete information process, which includes the disclosure of information and its comprehension[19], is the condition for providing a valid consent[20]. Consent to vaccine research has on an ethical level important implications with the concept of solidarity, as vaccination in general is intended as the willingness to accept costs (at least some risks) to assist others[21].

In emergency contexts, to the extent possible, all ethical requirements for conducting clinical research should be respected. Participants should be protected through a balancing of risks and potential benefits, always respecting the general principle of biomedical research, of the priority of the rights and interests of individual research subjects, as stated in the WMA Declaration of Helsinki, art. 8, and in the Oviedo Convention Additional Protocol, art. 3[22]. For research in emergency situations, such as the case of epidemics or moreover pandemic, specific ethical orientations are included in the CIOMS 2016 International Ethical Guidelines for Health-related Research Involving Humans, Guideline 20, "Research in Disasters and Disease Outbreaks", where we can read: "Conducting research in these situations raises important challenges such as the need to generate knowledge quickly, maintain public trust, and overcome practical obstacles to implementing research. These challenges need to be carefully balanced with the need to ensure the scientific validity of the research and uphold ethical principles in its conduct" (CIOMS, Guideline 20). The Guideline underlines that, without scientific validity, research lacks social value and must not be conducted[23]. When facing a serious, life-threatening infection, many people are in fact willing to assume high risks and use unproven agents within or outside of clinical trials. However, it is essential that investigators and sponsors realistically

[18] This can happen because of an overestimation of envisaged benefits deriving from participating in a clinical trial and/or due to misunderstandings concerning clinical research procedures (e.g. about randomization and/or the role of placebos in clinical trials).

[19] T.L. BEAUCHAMP, J. F. CHILDRESS, *Principles of biomedical ethics, 4th ed. Oxford University Press*, New York, 1994. The i-CONSENT project final guidelines provided specific recommendations on informed consent intended as a process, see I-CONSENT CONSORTIUM, *Guidelines for Tailoring the Informed Consent Process in Clinical Studies*, Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (FISABIO), Generalitat Valenciana, 2021, https://i-consentproject.eu/wp-content/uploads/2021/03/Guidelines-for-tailoring-the-informed-consent-process-in-clinical-studies-2.pdf (last accessed June 9th, 2021).

[20] UNESCO INTERNATIONAL BIOETHICS COMMITTEE (IBC), Report of the International Bioethics Committee of UNESCO (IBC) on Consent, UNESCO, 2008, n. 34 and n. 40.

[21] B. PRAINSACK, A. BUIX, *Solidarity: reflections on an emerging concept in bioethics, A report for The Nuffield Council on Bioethics*, 2005, https://www.nuffieldbioethics.org/assets/pdfs/Solidarity-report.pdf (last accessed June 9th 2021), p. 49.

[22] "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects" (WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki. Ethical principles for medical research involving human subjects*, 1964 (last revision 2013), art. 8, https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/DeclarationofHelsinki) (last accessed May 31st 2021); "The interests and welfare of the human being participating in research shall prevail over the sole interest of society or science" (COUNCIL OF EUROPE, *Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research* (ETS No. 195), 2005, art. 3, Primacy of the human being, https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/195) (last accessed May 31st 2021).

[23] COUNCIL OF INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCE (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, cit., Guideline 20: Research in disasters and disease outbreaks.

assess the potential individual benefits and risks of experimental interventions and communicate these clearly to potential participants and individuals at risk. Investigators, sponsors, international organizations, research ethics committees and other relevant stakeholders should ensure that the individual informed consent of participants is obtained even in a situation of duress, unless specific conditions for a waiver of informed consent are met[24].

International documents and guidelines include clear ethical orientations for research during emergencies or disease outbreaks. Again, in specific relation to the pandemic context, as underlined by the EMA, it is important to keep in mind that vaccines for Covid-19 are being developed, evaluated and approved according to current ethical and regulatory guidelines and requirements[25]. In the perspective of the ethical framework of international documents and guidelines include clear ethical orientations for research during emergencies or disease outbreaks, of the specific principle just mentioned and set up by the EMA, we consider of value to recall here altogether ethical principles included in several international guidelines. As far as vaccine trials in the pandemic context are concerned there are some specific ethical issues with implications for informed consent, and they are the following: (1) vaccine safety, including risk and potential benefits assessment for participants; (2) issues related to the involvement of healthy volunteers, including fair selection of study participants; (3) the use of a placebo, when there are vaccines already approved for emergency use; (4) the gratuity of the act of participants in the study. These specific ethical issues have implications for the informed consent and should clearly result in the informed consent process, as we will see in detail in the following sections.

2.1. Vaccine safety, including risk and potential benefits assessment for participants

As in translational research in general, where there is the need of making research in lab and clinical research closer to (even indirect) therapeutic good of patients, in vaccine research in the pandemic context, the most significant ethical issues derive from the risk of the intention to shorten the timeframes for the application of the results of the research. The first ethical requirement is to ensure the supply for safe, effective, available and affordable vaccines, which means research and clinical trials that comply with sound scientific methodology. The UNESCO Ethics Committees' call for global vaccines equity and global solidarity, includes a section on the ethical concerns for research on vaccines[26]. During the Covid-19 pandemic, ethically sound fast track in research on vaccines is

[24] COUNCIL OF INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCE (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, Guideline 10, Modifications and waivers of informed consent: "A research ethics committee may approve a modification or waiver of informed consent to research if: f the research would not be feasible or practicable to carry out without the waiver or modification; if the research has important social value; and if the research poses no more than minimal risks to participants. Additional provisions may apply when waivers or modifications of informed consent are approved in specific research contexts".

[25] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring (last accessed May 31st 2021).

[26] In facing the need of accelerating research to counteract the pandemic, the IBC underlines that: "The enormous pressure to find a vaccine should not impact the time needed to ensure the quality of the result and the primacy of safety and wellbeing of each participant during trials. The same is true for regulators, who should not compromise the quality of their evaluation and follow-up during the transition from the experimental phase toward the

compressed in time, applying the extensive knowledge on vaccine production gained with existing vaccines[27]. On this issue, the Italian Committee for Bioethics underlined that "Differently the possible shortening of the timeframe of trials can take place by allowing the vaccine a fast track, simplifying the administrative procedures for the review of research, eliminating administrative and bureaucratic inefficiencies"[28].

The WHO in the document "Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D"[29] recommended that prospective research participants must be able to weigh the risks and benefits of participation. This can be particularly challenging in a public health emergency because of uncertain risks and the perception that any research-related intervention must be 'better than nothing'. The WHO reminded that investigators and review bodies have an obligation to ensure that research activities do not proceed unless there is a reasonable scientific basis to believe that the study intervention is likely to be safe and efficacious and that risks to participants have been minimized to the extent reasonably possible. An ethical requirement of all clinical research is to minimize risk and maximize benefit: the EU's pharmaceutical legislation ensures that vaccines are only approved after scientific evaluation has demonstrated that their overall benefits outweigh their risks[30].

Safety requirements, which usually are assessed by an Independent Ethics Committee[31], go hand in hand with harmonized regulatory effort for the development of safe vaccines in the COVID-19 pandemic context (see following par.). The evaluation of safety of SARS-CoV-2 vaccines follows the

industrial-scale production and distribution" (UNESCO International Bioethics Committee (IBC) and the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), *UNESCO's Ethics Commissions' Call for Global Vaccines Equity and Solidarity. Joint Statement*, February 24th 2021, §3, https://unesdoc.unesco.org/ark:/48223/pf0000375608, last accessed May 31st 2021, §2). In the same line the Italian Committee for Bioethics, which recommended that the emergency should not in any case reduce research timing nor jump any phase of the research (Italian Committee for Bioethics, *Vaccines and Covid-19: ethical aspects on research, cost and distribution*, Opinion, November 27th 2020, § 2).

[27] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring (last accessed June 9th, 2021).

[28] Italian Committee for Bioethics, *Vaccines and Covid-19: ethical aspects on research, cost and distribution*, Opinion, November 27th 2020, § 2.

[29] WHO, *Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D*, 2020, https://apps.who.int/iris/bitstream/handle/10665/331507/WHO-RFH-20.1-eng.pdf?sequence=1&isAllowed=y&ua=1 (last accessed June 9th, 2021).

[30] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring (last accessed June 9th, 2021).

[31] Council of International Organizations of Medical Science (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, Guideline 23, *Requirements for establishing research ethics committees and for their review of protocols*. All decisions to adjust clinical trial conduct should be based on a risk assessment by an Independent Ethics Committee and trial participant safety always prevails (European Medicines Agency (EMA), *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic*, version 4, 04/02/2021, section 5, Risk assessment. The document is https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf (last accessed June 9th, 2021).

standard principles outlined in EMA guidance documents[32]. When experimental vaccines are tested for the first time in human subjects (during phase I trials or first-in-man trials), relevant risk assessment for first-in-human clinical studies means careful design and conduct of studies that reduce potential risk to humans, with special carefulness concerning benefit/risk assessment, that should clearly result in the informed consent process.

A vaccine's benefits in protecting people against Covid-19 must be far greater than any side effect or potential risks. At the same time, explaining the risk/benefit is very complex also because it may vary according to setting, age group. The level of acceptability of risks may vary depending on the expected benefits and the circumstances. Shortening times for study design, evaluation and implementation is not necessarily incompatible with maintaining adequate standards of reliability and scientific rigour but can reduce the probability of detecting rare side-effects and the possibility of analysing long-term effects. Participants manifesting an adverse reaction following the administration of the vaccine in different trial phases, including Phase 4, are entitled to a fair compensation[33].

In the risk and benefit assessment the probability that an adverse event occurs is a critical element that should be taken into account. It may happen that a severe event following immunization is possible, but its probability is extremely low; probability can be calculated in consideration of the appropriate sample size (rare events cannot be seen in studies with small sample size). "In special situations (for instance serious diseases for which there are no efficacious therapies available and epidemic situations), risk levels that would be unacceptable in other circumstances are permitted. Striking this balance is made difficult by the unpredictability that characterises all research. In this context, it is dutiful to guarantee special protection for individuals in conditions of particular vulnerability"[34]. As the main focus remains on safety, especially in in Phase I-II of vaccine trials, in the informed consent process the possibility of an overestimation of vaccine efficacy in general and in particular in placebo-controlled studies should be carefully prevented by a clear communication of by the researcher and the research team[35], including the explication of the concept of statistical variability, the probability that an adverse reaction occurs and the determination of vaccine efficacy.

[32]See EUROPEAN MEDICINES AGENCY (EMA), *Considerations on COVID-19 vaccine approval*, European Medicines Agency, Amsterdam, https://www.ema.europa.eu/en/ema-considerations-covid-19-vaccine-approval (last accessed June 9th, 2021).

[33] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*. Version of February 18, 2021, Istituto Superiore di Sanità, Roma, 2021. (Rapporto ISS COVID-19 n. 3/2021 - English version), p. 29, https://www.iss.it/documents/20126/0/Rapporto+ISS+COVID-19+3_2021_EN.pdf/ccb10ed0-c19f-3161-7ac9-44c7159d6e4c?t=1617880340241 (last accessed May 31st 2021). Insofar, as the regulatory procedures adopted for anti-COVID-19 vaccine trials have enabled the approval of new products in a short period of time, it is important to provide for prospective studies of the safety thereof, also setting forth that vaccine manufacturers must undertake to perform prospective follow-up studies for an adequate length of time.

[34] C. PETRINI, L. MINGHETTI, S. BRUSAFERRO, *A few ethical issues in translational research for medicinal products discovery and development*, cit., p. 489.

[35] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*, number 23 and 30.

2.2. Issues related to the involvement of healthy volunteers, including a fair selection of study participants

Being vaccine prophylactic agents, are generally given to healthy individuals. The involvement of healthy volunteers in a large number is another key issue related to vaccine research[36]. In vaccine research, individuals are asked to accept risk for the public good and the prospect of "provisional" benefit: individual benefit is "provisional" because individuals benefit directly from investigational vaccines only if they are sufficiently exposed to the infectious agent at some future time, had received the active vaccine and had been sufficiently protected[37]. In vaccine research, most risk accrues to individual participants and benefits accrue mainly to the community in finding a safe and protective vaccine[38].

General orientations for the obtaining of informed consent are valid for patients and for healthy volunteers[39] as well and encompass that the risk of undue influence should be careful assessed in obtaining informed consent. In addition, participants' understanding of the risks should be carefully assessed. Investigators should be able to identify any healthy participants that are not fully aware of the risks of the study; they should ensure as well that the potential participant is not taking part in another clinical trial at the same time and is not motivated by reimbursement. Core contents of comprehension should be understanding of risks, benefits and the determination of vaccine efficacy; that participation is not compulsory and that they can withdraw at any time. To achieve this, the information in the consent process should be adjusted to meet the needs of those with low literacy levels[40] and should be disclosed in culturally and linguistically appropriate ways[41].

Healthy volunteers should be carefully selected following inclusion and exclusion criteria. Scientifically, those most appropriate for vaccine efficacy studies are populations with a sufficient and predictable incidence of the disease in question to be able to show the effect of the vaccine. The sample size needed to demonstrate vaccine efficacy is usually large and is calculated in part on expected incidence,

[36] C. GRADY, *Ethics of vaccine research*, cit., p. 465.

[37] C. GRADY, *Ethics of vaccine research*, cit., p. 465. Unlike enrolled patients in trials for COVID-19 treatments, for healthy volunteers taking part to vaccine trials, the potential benefit is immunization, but healthy participants are exposed to a risk that they would not had if not participating in a trial.

[38] C. GRADY, *Ethics of vaccine research*, cit., p. 467.

[39] On the inclusion of healthy volunteers in clinical trials, the International Bioethics Committee in 2008 recalled that "in dealing with healthy volunteers, the significant fact is that those persons have not, in the first place, requested care/involvement in a medical procedure. They agree to be part of research, either for altruistic reasons or to seek compensation in some other way. The risks involved in the research should be minimized. A description of the research procedures, known risks, uncertainties and participant responsibilities should be provided in order to achieve informed consent. Undue incentives should not be offered to participants and adequate insurance covering adverse events and outcomes should be provided. Participation should be described in precise terms in writing and written informed consent should be mandatory" (UNESCO INTERNATIONAL BIOETHICS COMMITTEE (IBC), *Report On Consent*, 2008, n. 42 https://unesdoc.unesco.org/ark:/48223/pf0000178124, last accessed May 31st 2021).

[40] THE I-CONSENT CONSORTIUM, *Guidelines for tailoring the informed consent process in clinical studies*, cit., fact sheet IX: *The informed consent process in clinical research involving healthy participants*.

[41] C. GRADY, *Ethics of vaccine research*, cit., p. 467.

taking into account previous and evolving incidence of infection, demographics of the target population and characteristics of those who are likely to volunteer[42].

In addition, the WHO, in in the document *Ethical standards for research during public health emergencies*. *Distilling existing guidance to support COVID-19 R&D*[43] underlined the following aspects: "Participants should be treated with equal respect. They should be selected in such a way that minimizes risk, protects (but does not exclude) vulnerable populations, maximizes social value and collaborative partnerships, and does not jeopardize the scientific validity of the research. Pregnant women, minorities, children, and other groups considered to be "vulnerable" should not be routinely excluded from research participation without a reasonable scientific and ethical justification. Any exclusion from participation in research should be justified by robust and current scientific evidence, such as an unfavorable benefit-risk ratio". Vulnerable groups should be carefully protected but not excluded from the possibility of potential immunization and should not be underrepresented in vaccine research. In general it is important that population participating in the research, or the group represented by the population, could benefit of research results from the experimental protocol[44].

It would be worth recalling that in 2017 the EMA, as regards to the choice of participants in first-in-human trials, recommended specific clinical factors to consider in the decision to conduct a study in healthy volunteers, which are valid also in the pandemic context. The key inclusion and exclusion criteria for trials involving healthy participants should consider an adequate set of vital signs (including ECG), laboratory values and clinical assessments that should be within normal ranges. Deviations outside these ranges may be possible if justified[45]. Protocol violations may occur by accident and should be tracked. Following the EMA Guideline, it should be added that the choice of subjects (healthy volunteers as well as patients), among other ranges, includes a patient's ability to benefit from other products or interventions, the predicted therapeutic window of the Investigational Medical Product, and factors relating to special populations, including age, gender, ethnicity and genotype(s). A balanced and reasonable approach for first-in-human studies of a novel drug or vaccine candidate is crucial to ensure safety of trial participants. The principles of the EMA guideline need to be applied in a reasonable and scientific way based on how prophylactic and therapeutic vaccines against infectious diseases function.

2.3. The use of a placebo

In general, as known, the use of placebo is ethical only in absence of proven interventions, or if there are compelling scientific reasons for using it and delaying or withholding the established effective

[42] C. GRADY, *Ethics of vaccine research*, cit., p. 467.

[43] WHO, *Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D*, 2020, https://apps.who.int/iris/bitstream/handle/10665/331507/WHO-RFH-20.1-eng.pdf?sequence=1&isAllowed=y&ua=1 (last accessed May 31st 2021).

[44] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*, cit.

[45] EUROPEAN MEDICINES AGENCY (EMA), COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP), *Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products*, Rev. 1 (current version), § 8.2.3, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf (last accessed May 31st 2021).

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intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, as stated in the CIOMS 2016 Guideline 5 on the Choice of control in clinical trials. However, this is not the case of experimental vaccine trials which are deemed highly efficacious against a disease without a validated treatment; in vaccine trials a placebo group is essential to provide precise estimates. As far as experimental vaccines are being approved, the use of placebo makes easier the knowledge about vaccine efficacy and the report of adverse events; on the other side, avoiding to include a placebo group may jeopardize the clinical study.

However, it is necessary to distinguish from already existing trials, where it is deemed ethical to continue using placebo, and new study designs. At the end of 2020, the WHO issued a policy brief "Ethical considerations for current and future COVID-19 placebo-controlled vaccine trials and trial unblinding"[46], underlining that in the case of experimental vaccines granted of an Emergency Use Designation (EUD), it is ethical to continue placebo controlled studies: participants of COVID-19 vaccine trials should be advised that the issuance of emergency use designation by regulators to a candidate vaccine is based on early interim findings and is time-limited in nature. Should a candidate vaccine attain EUD in a setting hosting a COVID-19 vaccine trial, investigators should explain the scientific benefit of continued trial participation (which is about duration of protection), the clinical factors that support the participant's administration of the EUD vaccine outside the trial, and the implications of unblinding, to trial participants immediately eligible to access the EUD vaccine. Following such counselling, such participants should be offered the opportunity to be unblinded so they may make an informed choice about whether to access the EUD vaccine programmatically as soon as practically possible, should they wish to do so. If such participants request unblinding (and theoretically they can request to receive the "active" vaccine), investigators and sponsors have an ethical duty to abide their request. This will necessitate the development of an appropriate engagement, communications, and dissemination strategy to explain unblinding eligibility criteria and the implications of unblinding for trial participants. Should a participant opt to withdraw from a trial, their follow-up could continue as part of an observational study, should they agree. Trial participants who are not deemed to be at significant risk of COVID-19 infection or mortality and who do not meet prevailing eligibility criteria to access a candidate vaccine granted EUD, should be informed of the scientific benefits of continuing with the trial and encouraged to remain enrolled – while fully acknowledging their right to withdraw from a trial at any point, without penalty. The continued enrolment of as many participants as possible, for as long as possible, will have significant scientific and public health value, as doing so will yield invaluable data to enable regulatory decision-making regarding product registration / licensure. The WHO Working group on placebo controlled vaccine trials supported this position: "While vaccine supplies are limited, available vaccines are still investigational, or public health recommendations to use those vaccines have not been made, we believe it is ethically appropriate to continue blinded follow-up of placebo recipients in existing trials and to randomly assign new participants to vaccine or

[46] WHO, *Access to COVID-19 Tools (ACT) Accelerator Ethics & Governance Working Group, Emergency use designation of COVID-19 candidate vaccines: ethical considerations for current and future COVID-19 placebo-controlled vaccine trials and trial unblinding*, Policy brief, December 18th, 2020, https://www.who.int/publications/i/item/emergency-use-designation-of-covid-19-candidate-vaccines-ethical-considerations-for-current-and-future-covid-19-placebo-controlled-vaccine-trials-and-trial-unblinding (last accessed May 31st 2021).

placebo. Moreover, under these conditions, we believe that trial sponsors are not ethically obligated to unblind treatment assignments for participants who desire to obtain a different investigational vaccine. People who enroll in clinical trials for altruistic reasons would probably understand the value of gathering data that will further elucidate the safety and efficacy of these vaccines and their appropriate use"[47].

As regard to new trials for vaccines against Covid-19 when another vaccine is authorized, the Italian National Institute of Health (ISS) Bioethics Covid-19 Working Group delivered specific recommendations on the use of placebo in vaccine trials, when one or more vaccines have already been validated, writing: "when there is a vaccine capable of protecting trial participants, it becomes unethical to subject them to the risk of contracting the disease. However, ongoing studies should not be interrupted, as at the time of enrolling in the study, trial participants accepted the risks of participating, although they should nonetheless be informed of the possibility of either continuing or interrupting their participation. For new clinical trials, it is difficult to see any other ethically acceptable option than comparative study models comparing new products to already approved vaccines. This will require a total revision of the anti Covid-19 vaccine trials, consequently delaying the possibility of achieving other good vaccines"[48].

2.4. The gratuity of the act of participants in the study

Last but not least, a crucial ethical issue is the emphasis that should be given to the gratuity of the act. Any form of payment or improper incentive, both direct or indirect, to participants, must be excluded; similar acts may induce poor people to expose themselves to risks for purely economic objectives, as the Italian Committee for Bioethics recently advised: "Taking into account the exceptional nature of the contingency, if, in order to implement urgent measures for the protection of participants in a clinical study, expenses are expected to be borne by them, similarly to what is already allowed in extraordinary cases (for example studies on rare diseases), the sponsor is allowed to reimburse these expenses to the subjects. The expenses incurred must be adequately documented and risk coverage must be guaranteed. Once the reliability and ability to protect against the disease have finally been proven, the vaccine will have to undergo assessment and then approval by the regulatory authorities and its effectiveness verified over time"[49]. In vaccine research, as in clinical research in general, participants should be reasonably reimbursed for costs directly incurred during the research, such as travel costs, and compensated reasonably for their inconvenience and time spent but the gratuity of the act should remain clear and be transparently conveyed in the informed consent: it should be clear that there is no financial compensation for the participation in a study, as it could unduly influence the decision of participating in a trial[50].

[47] WHO AD HOC EXPERT GROUP ON THE NEXT STEPS FOR COVID-19 VACCINE EVALUATION, *Placebo-Controlled Trials of Covid-19 Vaccines — Why We Still Need Them*, The New England Journal of Medicine, 384;2, published online on January 14, 2021, pp.3, https://www.nejm.org/doi/full/10.1056/NEJMp2033538 (last accessed May 31st 2021).
[48] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19*, cit., pp. 30-31.
[49] ITALIAN COMMITTEE FOR BIOETHICS, *Vaccines and Covid-19: ethical aspects on research, cost and distribution*, Opinion, November 27th, 2020, §2, pp. 6-7.
[50] THE I-CONSENT CONSORTIUM, *Guidelines for tailoring the informed consent process in clinical studies*, cit., fact sheet IX: *The informed consent process in clinical research involving healthy participants*.

3. Regulatory issues in vaccine research in the pandemic context: implications for informed consent

The already mentioned Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine[51] states important principles and rules of biomedical research such as the primacy of the human being, equitable access to health care and the requirement of respecting professional standards. In line with the Declaration of Helsinki, the Convention states free and informed consent as a fundamental condition of any intervention in the health field. The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research[52] covers the full range of research activities in the health field involving interventions on human beings, stating the independent examination by an ethics committee (independent and previously informed with all the elements related to the research to be approved); legal requirements for the information for research participants are stated in the additional protocol as well as those regarding consent.

On an international level, the WHO Emergency Use Listing Procedure (EUL) is a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics with the ultimate aim of expediting the availability of these products to people affected by a public health emergency. This procedure assists interested UN procurement agencies and Member States in determining the acceptability of using specific products, based on an essential set of available quality, safety, and efficacy and performance data; the procedure is a key tool for companies wishing to submit their products for use during health emergencies. In addition, the Strategic Advisory Group of Experts on Immunization (SAGE) is charged with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. The Global Advisory Committee on Vaccine Safety (GACVS) has recommended that any review of the safety of new vaccines be based on these templates as they offer a structured approach to evaluating safety. The templates are currently being completed by some of the Covid-19 vaccine developers, especially for the vaccines in an advanced phase of clinical trials[53].

In the regulatory landscape, during the ongoing Covid-19 pandemic, the International Coalition of Medicines Regulatory Authorities (ICMRA) is acting as a forum to support strategic coordination and international cooperation among global medicine regulatory authorities, and is in order to harmonize as much as possible regulatory efforts. The aim of all these activities has been (and is) to expedite and streamline the development, authorization and availability of Covid-19 treatments and vaccines worldwide. ICMRA members also work towards increasing the efficiency and effectiveness of regulatory processes and decision-making. Following ICMRA provisions, many countries have adopted

[51] The Council of Europe, *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (ETS No. 164), 1997, https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164 (last accessed May 31st 2021).

[52] The Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research* (ETS No. 195), 2005, https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/195 (last accessed May 31st 2021).

[53] WHO, *Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines, Background paper on Covid-19 disease and vaccines*, 22 December 2020, https://apps.who.int/iris/handle/10665/338095 (last accessed April 15th 2021).

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regulatory flexibility in order to speed up authorization procedures for vaccines always basing on sound scientific information as regard to safety and efficacy. Regulatory flexibility mainly affects procedures for vaccine evaluation and emergency approval and it assumes international harmonized regulatory requirements for Good Clinical Practice[54] and in the European Union the legal context of the Regulation (EU) No. 536/2014 of the European Parliament and of the Council of the 16 April 2014 on clinical trials for human use, and repealing Directive 2001/20/EC.

In the EU all clinical trials, including vaccine trials, are governed by the Regulation No 536/2014 which within its main goals encompasses creating an environment that is favourable to conducting clinical trials in the EU, with the highest standards of safety for participants and increased transparency of trial information. Today the EU legal framework for medicinal products for human use[55] guarantees high standards of quality and the safety of medicinal products, while promoting the good functioning of the internal market with measures that encourage innovation and competiveness. All these rules are valid also in emergency contexts. In addition, the European Commission has supported since June 2020 the acceleration of development, manufacturing, and deployment of vaccines against Covid-19, always respecting sound scientific criteria, through the "EU strategy for COVID-19 vaccines". The strategy has the following objectives: a) ensuring the quality, safety and efficacy of vaccines; b) securing timely access to vaccines for Member States and their population while leading the global solidarity effort; c) ensuring equitable access for all in the EU to an affordable vaccine as early as possible. When taking the financing decision, among other non-exhaustive criteria mentioned in the document, it should be taken into account the soundness of scientific approach and technology used, including drawing on any evidence related to quality, safety and efficacy already generated from the development phases, where available.

As part of its health threat plan activated to fight Covid-19, the European Medicines Agency has finalized and published the composition and objectives of its Covid-19 EMA pandemic Task Force (COVID-ETF), which assists Member States and the European Commission in dealing with development, authorization and safety monitoring of therapeutics and vaccines intended for treatment or prevention of Covid-19. The main purpose of the COVID-ETF is to draw on the expertise

[54] As known, Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that clinical-trial data are credible. See INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH), E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), last revision 2018, https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice (last accessed May 31st 2021); WHO, *Handbook for Good Clinical Research Practice (GCP). Guidance for implementation*, World Health Organization, 2002, https://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf (last accessed June 9th, 2021); see also the section on Good clinical practice at the EMA website: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice (last accessed June 9th, 2021).

[55] The rules governing medicinal products in the European Union include the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use; the Council Directive 89/105/EEC, of 21 December 1988, relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems; the Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (the consolidated version dated 28/01/2019).

of the European medicines regulatory network and ensure a fast and coordinated response to the Covid-19 pandemic. The task force is accountable to EMA's human medicines committee (CHMP) for all its activities. Strict rules are in place to assure the independence of all members. In November 2020, the Committee for human medicinal products (CHMP) issued the document "EMA considerations on Covid-19 vaccine approval"[56] following key principles of trial design for Covid-19 agreed by the EMA and international medicines regulators (ICMRA). Procedures are in place to allow rolling review of the quality, nonclinical and clinical data as they are submitted to EU regulators. The governance of the EMA in the context of regulatory flexibility is outlined in the 25 March 2021 document "EMA Initiatives for acceleration of development support and evaluation procedures for Covid-19 treatments and vaccines" and include EMA's rapid formal review procedures related to Covid-19, namely: rapid scientific advice; rapid agreement of a paediatric investigation plan and rapid compliance check; rolling review; marketing authorization; extension of indication and extension of marketing authorization; compassionate Use. Rapid scientific advice is provided in support of evidence generation planning for treatments and vaccines for Covid-19. It is an ad hoc procedure which follows the general principles of the regular scientific advice but with adaptations to facilitate acceleration. The advice will be adopted by the CHMP, but the process will also involve the COVID-ETF. Rapid scientific advice is provided in support of evidence generation planning for treatments and vaccines for Covid-19. It is an ad hoc procedure which follows the general principles of the regular scientific advice but with adaptations to facilitate acceleration. The advice will be adopted by the CHMP, but the process will also involve the COVID-ETF. Rolling Review is as well an ad hoc procedure used in an emergency context to allow EMA to continuously assess the data for an upcoming highly promising application as they become available, i.e. preceding the formal submission of a complete application for a new marketing authorization (or for an extension of indication in case of authorized medicines). Through this process, EMA will be able to complete the review of marketing authorization application dossier earlier while ensuring robust scientific opinions. Such rolling reviews are conducted under the EMA emerging health threats plan and starting them requires specific agreement by the COVID-ETF, which also acts as forum for discussion on the rolling data assessment.

While the unprecedented scenario of the pandemic requires special considerations on the regulatory requirements for approval, the benefits and risks of Covid-19 vaccines need to be properly assessed based on detailed information on manufacturing, nonclinical data and well-designed clinical trials. Key aspects of regulatory procedures should be conveyed in the informed consent process in order to inform participants of specific procedures for conducting clinical trials in the pandemic context, explaining as appropriate the focus on participants' safety and protection.

4. The case of human challenge studies for vaccine against Covid-19: ethical issues and implications for informed consent

In the context of vaccine research, highly sensitive ethical issues can arise from the so-called "human challenge studies", which are studies that concern intentionally infecting healthy subjects in order to

[56] European Medicines Agency (EMA), Committee for human medicinal products (CHMP), *EMA considerations on COVID-19 vaccine approval*, cit.

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accelerate the study of vaccine efficacy, or more in general to investigate a disease functioning or test possible treatments. During human challenge studies (HCS) (also known as "controlled human infection", CHI studies) for an experimental vaccine, healthy volunteers receive an experimental vaccine, and are deliberately exposed to the pathogen. Challenge studies have a long history[57], which goes back to the process of the discovery of first vaccines[58].

The topic raised interests again in the current pandemic context as it has been advanced the proposal to test experimental vaccines against Covid-19 namely through human challenge studies[59]. All along 2020, a large debate raised in the scientific literature on the issue of human challenge studies discussing their ethical conditions. Although there we cannot enter in detail in reporting the debate, the discussion focused on different positions[60].

Some authors have argued in favor of the possibility of exposing full-informed healthy participants at certain (including high) risks in consideration of the possibility to reduce global burden/overall harm from the virus[61] or for the social value of research[62] or at least adopting some mitigation strategies[63]. These positions raise as well ethical issue. In fact, other authors underlined that social value and fair selection of participants in HCS could not be in any case scientifically sound, therefore not justifying participants' risk exposure[64]; in addition, high uncertainty of scientific information on Covid-19 could undermine the validity of informed consent[65]. Human challenge studies reveal as an "epistemic shortcut"[66], and ultimately they cannot be conducted in an ethical manner[67].

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[57] J. H. SOLBAKK ET AL., *Back to WHAT? The role of research ethics in pandemic times*, in Medicine, Health Care and Philosophy, published online on November 3, 2020, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7607543/pdf/11019_2020_Article_9984.pdf (last accessed June 9th, 2021).

[58] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*, cit.

[59] N. EYAL ET AL., *Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure*, in The Journal of Infectious Diseases, 2020;221:1752–6.

[60] As an example, O'NEILL MC PARTLIN ET AL., *Covid-19 vaccines: Should we allow human challenge studies to infect healthy volunteers with SARS-CoV-2?,* in British Medical Journal 2020;371, includes arguments for and against human challenge studies for Covid-19 vaccines.

[61] See N. EYAL ET AL., *Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure*, cit.; R. CHAPPELL, P. SINGER, *Pandemic ethics: the case for risky research*, in *Research ethics*, 2020, Vol. 16(3-4), 1-8.

[62] See S. SHAH ET AL., *Ethics of controlled human infection to address COVID-19*, in Science 368 (6493), 832-834; G. OWEN SCHAEFER ET AL., *COVID-19 vaccine development: Time to consider SARS-CoV-2 challenge studies?,* in *Vaccine* 38 (2020), pp. 5085-5088.

[63] See A. RICHARDS, *Ethical guidelines for deliberately infecting volunteers with COVID-19*, in *Journal of Medical Ethics*, 2020, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7316118/pdf/medethics-2020-106322.pdf (last accessed May 31st 2021); namely conditions would be addressing: 1) the risk of harm to participants, 2) the potential of no useable vaccine, 3) the validity of consent, 4) reputational risk, 5) the slippery slope.

[64] See S. HOLM, *Controlled human infection with SARS- CoV-2 to study COVID-19 vaccines and treatments: bioethics in Utopia*, Journal of Medical Ethics, online preprint publication, June 2020, 1-5.

[65] See A. KEREN, O. LEV*, Uncertainty, error and informed consent to challenge trials of COVID-19 vaccines: response to Steel et al.*, online preprint publication, August 2020, 1-2, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7482142/pdf/medethics-2020-106793.pdf (last accessed May 31st 2021).

[66] J. H. SOLBAKK ET AL., *Back to WHAT? The role of research ethics in pandemic times*, cit.

[67] L. TAMBORNINO, D. LANZERATH, *COVID-19 human challenge trials – what research ethics committees need to consider*, in Research Ethics, Vol. 16(3-4), 2020, 1–11. The Authors consider unethical to conduct human challenge studies for Covid-19 vaccines. In addition, they suggest three important points that should be considered by REC

Even if the HCS design could in principle accelerate Covid-19 vaccine development, as requiring far fewer volunteers than a typical study, needing less time in order to obtain information about vaccine efficacy, and accelerating possible comparative evaluation among vaccines, there are important ethical considerations that must be addressed. In addition to the issues raised by vaccine research in general, highly sensitive ethical issues in the case of HCS mainly regards participants' safety and protection. As a general requirement, the CIOMS 2016 Guidelines, in the Commentary on Guideline 4, Potential individual benefits and risks of research, underline that the risk implied by infecting healthy volunteers is in any case not proportionate[68].

As regard to the specific case of HCS for a vaccine against Covid-19, due to the fact that pathogenesis of Covid-19 is currently poorly understood and in consideration of the absence of validated therapies, ethical issues that should be taken into account are the following:

a) participants would be exposed not to minimal risk but to high risk[69] (although risk depends on the fact – or not – that the same technology has already been used before) and thus, ultimately, considered as "experimental objects", therefore undermining the fundamental principle of clinical research[70]; it is not scientifically confirmed that HCS have sound scientific justification[71];
b) the information in the consent process could be undermined by high uncertainty of knowledge about COVID-19 disease[72] ;
c) a model of disease in healthy young volunteers may have questionable scientific validity when extrapolated to older or other at-risk populations that have disproportionate morbidity[73];

in evaluating these kinds of studies: 1. minimizing risks; 2. appropriate informed consent; 3. avoiding monetary inducements.

[68] See the COUNCIL OF INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCE (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, cit. With reference to the case of infecting with Ebola, the Commentary on Guideline 4 (Potential individual benefits and risks of research) stresses that "The ethical justification for exposing participants to risks is the social and scientific value of research, namely the prospect of generating the knowledge and means necessary to protect and promote people's health (see Guideline 1 – Scientific and social value and respect for rights). However, some risks cannot be justified, even when the research has great social and scientific value and adults who are capable of giving informed consent would give their voluntary, informed consent to participate in the study. For example, a study that involves deliberately infecting healthy individuals with anthrax or Ebola - both of which pose a very high mortality risk due to the absence of effective treatments - would not be acceptable even if it could result in developing an effective vaccine against these diseases. Therefore, researchers, sponsors, and research ethics committees must ensure that the risks are reasonable in light of the social and scientific value of research and that the study does not exceed an upper limit of risks to study participants".

[69] See J. H. SOLBAKK ET AL., *Back to WHAT? The role of research ethics in pandemic times*, cit., underlining that Covid-19 human challenge studies have a much higher risk than the minor risk threshold.

[70] See the interesting considerations on human challenge studies discussed by the already mentioned document ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*, cit.

[71] See C. WEIJER in S. O'NEILL MC PARTLIN ET AL., *Covid-19 vaccines: Should we allow human challenge studies to infect healthy volunteers with SARS-CoV-2?,* cit.; J. H. SOLBAKK ET AL., *Back to WHAT? The role of research ethics in pandemic times*, cit.

[72] See A. KEREN, O. LEV*, Uncertainty, error and informed consent to challenge trials of COVID-19 vaccines: response to Steel et al.*, cit.; O'NEILL MC PARTLIN ET AL., *Covid-19 vaccines: Should we allow human challenge studies to infect healthy volunteers with SARS-CoV-2?*, cit.

[73] See J. H. SOLBAKK ET AL., *Back to WHAT? The role of research ethics in pandemic times*, cit.

d) deliberating infecting volunteers would be an action in contrast with medical deontology and the principle of not to harm[74];
e) the participation of poorer people, e.g. from low-middle income countries, raises ethical concerns about exploitation and an unfair distribution of risk and benefit, in particular when medicines later are less available to populations who have contributed to their development through participation in the trials[75].

Importantly, in 2020 the WHO issued a new document on this issue[76], at least partially revising previous position expressed in 2016 in a document on the same topic[77]. The WHO 2016 document had recommended that a human challenge study to establish the challenge model should also match the same expectations for conduct of a vaccine study, accordingly being properly designed and conducted"[78]. Of note, the WHO underlined also that HCS would not be considered safe and ethical when the pathogen causes diseases with high mortality risks and in absence of therapies to prevent or ameliorate disease and preclude death. On a practical level, the WHO recommended that human challenge trials should have been undertaken in accordance with a protocol and in special facilities that are designed and operated in a manner that can prevent the spread of the challenge organism to people outside the study or to the environment. These clinical facilities should be capable of providing continuous monitoring and medical attention at the appropriate point(s) in time after the challenge is given.

It is worth recalling here[79] the WHO 2020 ethics requirements for HCS, highlighting as well the implications for informed consent. As a first general requirement, Covid-19 challenge studies must have strong scientific justification and as nonetheless ethically sensitive they must be carefully designed and conducted in order to minimize harm to volunteers and preserve public trust in research. Other key requirements are: consultation, engagement and coordination with the public, experts, funders, regulators, and policy makers; selection of study sites, in order to maintain the highest scientific, clinical, and ethical standards; a fair participant selection, implemented according to criteria aimed at limiting and minimizing risk; an expert review carried on by specialized independent committees; a rigorous informed consent process.

Safety of participants is a key necessary condition for the ethical acceptability of challenge studies. Participant selection criteria must be designed so that there is a high level of confidence that participation is as safe as possible. According to the WHO document, initial studies should thus be limited to young healthy adults, e.g., aged 18–30 years. Within these groups, selection criteria might prioritize those who face high background probability of infection (to the extent that this does not

[74] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*, cit., p. 27.
[75] WHO, *Key Criteria for the Ethical Acceptability of COVID-19 Human Challenge Studies*, cit.
[76] WHO, *Key Criteria for the Ethical Acceptability of COVID-19 Human Challenge Studies*, cit.
[77] WHO, *Human Challenge Trials for Vaccine Development: Regulatory Considerations*, 2016, https://www.who.int/biologicals/expert_committee/Human_challenge_Trials_IK_final.pdf (last accessed May 31st 2021).
[78] WHO, *Human Challenge Trials for Vaccine Development: Regulatory Considerations*, cit.
[79] L. PALAZZANI, *Informed consent in clinical trials in the context of the pandemic between bioethics and biolaw: a general overview*, cit., recalls these key arguments; see also ITALIAN COMMITTEE FOR BIOETHICS, *Vaccines and Covid-19: ethical aspects on research, cost and distribution*, cit.

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reflect background social injustice) because such participants would face less marginal risk and a potential for direct benefit (for example, if participation results in some degree of immunity to Covid-19, and participants are exposed to infection after completion of the study). Those whose background risk is high because of social injustice should be excluded from participation because their inclusion could be considered unethical exploitation (i.e., taking advantage of those who have already been wrongly disadvantaged). Any prospective participants who could reasonably be perceived to be vulnerable in other ways that would undermine their consent or put them at greater risk (for example, as a result of the mental health strain of inpatient isolation during the study) should also be excluded. Even with such criteria in place, participants may still face absolute risks or levels of uncertainty related to Covid-19 infection that might be higher than some other ethically acceptable "non-therapeutic" studies involving risk to healthy volunteers (for example, some phase I drug trials and many well established challenge studies), although still within acceptable upper limits to research risk.

With specific reference to the informed consent, the information processes should be particularly rigorous in Covid-19 challenge studies because of the heightened potential risks and uncertainties involved. Challenge studies should routinely incorporate tests of participant understanding during the informed consent process. Such tests are particularly important in SARS-CoV-2 challenge studies, and should be based on the best available data regarding risks (and uncertainties) as well as relevant evidence regarding how important and complex information should be conveyed to participants to maximize understanding. In addition, regarding consent, the WHO recommends that consent should be revisited throughout the study, as is often the case for other challenge studies. This should occur, for example, when new relevant data (for example, regarding risks) become available after the study has commenced, and immediately prior to challenge with Covid-19. Consent processes and participant selection criteria should be such that there is virtually no doubt that participants comprehensively understand the potential risks of participation and that consent is voluntary.

5. Conclusion: key aspects of the informed consent process in vaccine research in the pandemic context.

Basing on the information documented in this contribution, we offer there an indicative list of aspects to be included in a well-designed information and consent process for participants' in vaccine research in the Covid-19 pandemic:

1. potential trial participants should not be included in trials without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations and best scientific evidence[80];
2. the informed consent process should be developed at the best of current knowledge and must clearly communicate risks and uncertainties, including communication of statistical variability and probability that an adverse event occurs, alongside with potential benefits (in the case of vaccine, the expected but potential benefit is immunization);

[80] EUROPEAN MEDICINES AGENCY (EMA), *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic*, cit.

3. the information process should definitely not end with the signature on the informed consent form, but should continue in a bidirectional communication process[81], until the end of the study, as research regarding Covid-19 disease, treatments and vaccines speeds up very quickly and new information can arise, particularly concerning new emergency use approval of other vaccines[82]; to the extent possible, consent should be dynamic[83];
4. the content of information should meet ethical and regulatory requirements and mention specific issues related to vaccine trials, including:

   a) risk and benefits assessment;

   b) issues related to inclusion of healthy volunteers; In the case of vaccine trials, the potential benefit is immunization but healthy participants are exposed to a risk that they would not had if not participating in a trial. To this aim, participants' understanding of the risks should be carefully assessed; it should be underlined that participation is not compulsory and that participants can withdraw at any time;

   c) issues related to study design and the possibility of receiving a placebo; when new vaccines are approved for emergency use in the site of the clinical trial participants should be informed of this and asked if they are willing to continue in the trials with the possibility, if being part of the placebo group, of receiving the experimental vaccine in the end[84];

   d) the informed consent should clearly include the reference to the full compensation for any research-related harm; compensation should be determined avoiding unduly influence to the decision of participating in a trial, expecially in cases of subjects without a job[85].
5. unless linked to the implementation of urgent safety measures, changes in informed consent procedures will need to be reviewed and approved by the relevant ethics committee in advance[86];

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[81] THE I-CONSENT CONSORTIUM, *Guidelines for tailoring the informed consent process in clinical studies*, cit., section 1, *Consent as a process.*

[82] N. LURIE ET AL., *The Development of COVID-19 Vaccines. Safeguards Needed*, in JAMA, 324 (5), 2020, pp. 439-440.

[83] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*, cit., p. 24.

[84] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*, cit., p. 24; D. WENDLER ET AL., *COVID-19 vaccine trial ethics once we have efficacious vaccines*, in *Science*, published online December 3rd, 2020, https://science.sciencemag.org/content/early/2020/12/02/science.abf5084/tab-pdf?versioned=true (last accessed May 31st 2021). According to the Authors, "Researchers are ethically obligated to inform participants of developments that might influence their willingness to remain in a clinical trial. Clearly, that a vaccine candidate has been found to be safe and efficacious meets this standard. Hence, investigators should inform participants in all trials of such a finding. This information should include the vaccine's safety record, the level of protection it provides, the populations for which it has been found to be safe and efficacious, and whether it might be available through an Emergency Use Approval or other means".

[85] ISS BIOETHICS COVID-19 WORKING GROUP, *Ethical aspects in the testing of anti-COVID-19 vaccines*, cit., at p. 28 discusses this issue.

[86] EUROPEAN MEDICINES AGENCY (EMA), *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic*, version 4, 04/02/2021, par. 8: ("The informed consent procedure in all trials needs to remain compliant with the trial protocol as well as with EU and national legal framework. It is acknowledged that national

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6. investigators have an obligation to share information collected as part of a study if it is important for the ongoing response efforts, such as information about hidden cases and transmission chains or resistance to response measures. Persons who share the information and those who receive it should protect the confidentiality of personal information to the maximum extent possible. As part of the informed consent process, investigators should inform potential participants about the circumstances under which their personal information might be shared with public health authorities[87].

In addition to above mentioned critical aspects, as regard to the informed consent process in the case of human challenge trials for a vaccine against Covid-19, for an appropriate information it should be recommended:

1. highly sensitive ethical issues descripted in the WHO 2020 document "*Key Criteria for the Ethical Acceptability of COVID-19 Human Challenge Studies*" should be carefully considered in the design of the trial as well as in the preparation of the informed consent process;
2. volunteers should receive a very detailed description of risks that is fully up-to-date with current scientific knowledge. At present, this would include these four essential points[88]: 1) The long-term effects of a Covid-19 infection remain unclear; 2) Covid-19 infection can be fatal; 3) Research participants need to fully disclose their medical history to determine their risk exposure; 4) Research participants may not be able to withdraw immediately from a study that is set in an inpatient setting. In addition, participants should be informed also to risks that could affect their relatives (e.g., primarily, the risk of contagion and additional requirements for social distancing);
3. volunteers should be informed that the trial should be conducted in accordance with a protocol and in special facilities that are designed and operated in a manner that can prevent the spread of the challenge organism to people outside the study or to the environment. These clinical facilities should be capable of providing continuous monitoring and medical attention at the appropriate point(s) in time after the challenge is given;
4. potential participants should be afforded an appropriate reflection period before consenting[89], some authors suggest a three days' time and any form of inducement (including financial inducement) should be carefully avoided.

In conclusion, in the current pandemic, individual informed consent remains a key ethical requirement for participants' protection in vaccine research. In the informed consent process, in fact, alongside

provisions and approaches differ; Sponsors should be mindful of the current pressure on the medical profession; Trial participants should be informed by the investigator, in a timely manner, about changes in the conduct of the clinical trial relevant to them (e.g. cancellation of visits, change in laboratory testing, delivery of Investigational Medical Product)".

[87] WHO, *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks*, 2016, https://apps.who.int/iris/bitstream/handle/10665/250580/9789241549837-eng.pdf?sequence=1&isAllowed=y (last accessed May 31st 2021).

[88] L. TAMBORNINO, D. LANZERATH, *COVID-19 human challenge trials – what research ethics committees need to consider*, cit.

[89] A. RICHARDS, *Ethical guidelines for deliberately infecting volunteers with COVID-19*, cit.

with general requirements related to biomedical research should be conveyed ethical issues specific to experimental vaccine trials.

As much as ever, to fulfil ethical requirements, in the pandemic context informed consent needs to be considered in the wider "ethics ecosystem". The Nuffield Council on Bioethics stressed clearly this aspect in its 2020 extensive report on research in global health emergencies: "Consent alone is never a sufficient requirement for research to be ethically acceptable. Rather, it is one part of the wider 'ethics ecosystem' constituting and supporting ethical research conduct"[90]. This ecosystem includes responsibilities on the part of investigators and ethics committees to be confident that benefits and risks have been carefully scrutinized, risks justified, and wider questions of social justice and social value considered. The Report by the Nuffield Council formulates this requirement in a meaningful question that could be relevant for the different stakeholders (investigators, sponsors, ethics committee) of the consent process: "Can what is being asked of potential research participants be justified as fair, given the emergency circumstances they are facing?". The Report advances as well that the value of equal respect, understood with respect to individuals and to broader communities, can act as a guide in thinking through how other aspects of the ethics ecosystem can be strengthened in emergency contexts to ensure such respect is fully shown[91].

[90] THE NUFFIELD COUNCIL ON BIOETHICS, *Research in global health emergencies: ethical issues*, Report, January 28th, 2020, Chapter 7 – Consent an beyond: the wider ethics ecosystem. https://www.nuffieldbioethics.org/publications/research-in-global-health-emergencies (last accessed June 9th, 2021).

[91] THE NUFFIELD COUNCIL ON BIOETHICS, *Research in global health emergencies: ethical issues*, cit., § 7.8.

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Special issue

Informed consent, clinical research, Covid-19 and contact tracing apps: some neuroethical concerns

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ABSTRACT: The explosion of the Covid-19 pandemic has led us to introduce numerous states of exception in our everyday lives, sparking debates about their appropriateness at various levels. Among other changes we have adopted, there has been an increase of apps supporting our fight against Covid-19 all over the world. From apps helping us to join and coordinate clinical trials to contact tracing apps, various are the instances in which digital technology has -at least attempted to- come to rescue to the scientific, public policy and political realms during the challenging times we are currently living in. Particularly in relation to contact tracing apps, ethical concerns have been raised over the level of transparency that they can guarantee, often stressing how the State needs to ensure a number of variables to be granted to citizens: from privacy to fairness of access and distribution through their compulsory status or not. In Western liberal democracies, the assumption has been that all risks associated with this digital technology would have to be dealt with by the State -hence making its misuse "only" public, albeit authoritarian in their most dystopian versions. Here, the intention is to stress some of the overlooked dimensions of the use of different types of Covid-19 related apps. More specifically, this paper takes issue with the secondary use of data that various private companies engaged in the fight against Covid-19 could make -with an unclear role for informed consent. Especially when in the hands of private, for profit, companies, attention should abound on what states of exceptions we are allowing to slip through our ethical supervision -and to what we are actually giving consent to when downloading these apps.

KEYWORDS: Big data; contact tracing apps; Covid-19; informed consent; neuroethics

SUMMARY: 1. Clinical trials in relation to Covid-19 – 2. Contact tracing apps across the globe – 3. Behaviour and private companies – 4. Predicting or designing? – 5. Stimulating the brain while ensuring informed consent – 6. Determining who buys what? – 7. Concluding remarks.

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1. Clinical trials in relation to Covid-19

Aside from the centrality of the notion on informed consent highlighted by recent projects[1], clinical trials are historically conceived to be carried out in predefined and restricted settings (a decisive component for both constant supervision and scientific methodology), yet the advent of digital technology might have changed this paradigm quite substantially[2] . Contact tracing apps might have opened the Pandora box of a not-so-subtle revolution that occurred through the digitalization of clinical trials and data. To understand better the meaning of this affirmation, let us take an extract of the definition given of clinical trials by the US National Institute of Health on their website:

"Clinical trials are research studies performed in people that are aimed at evaluating a medical, surgical, or *behavioral* intervention."[3]

The interesting aspect highlighted here is that behaviour itself could be both the subject of the study and the goal of the trial. As it will explained more in details in the following sections of the paper, not only that behaviour has a very broad definition that encompasses many layers of individual and societal variables for which technology could represent an unprecedented tool to quantify and address them, but we also know that, through neuromarketing, the private sector has been studying for years now how to influence and reshape our behaviour. Covid-19 related apps could surely work towards a virtuous direction, raising hopes but also concerns of the appropriateness of certain collections of data -and the risk of polarizing us towards less noble behaviours.
Let us remember that, aside from being one of the two main types of clinical studies, a clinical trial can be interventional, where it is supposed to try out a possible intervention on the population -and this could include a medical device, a drug or, more relevantly here, a procedure. A clinical study can otherwise be "only" observational, where subjects are scrutinized in the light of a theory. Notably, these types of studies do not necessarily need to provide a treatment but are used to observe the theory in action and possibly readdress some deficiencies erupted by the implementation of a certain drug, treatment and so on. They are, by definition, less invasive both in terms of physical e psychological burden and people can be involved in more than one of them at the same time precisely for those reasons.
The need for enrolling patients during a pandemic has added additional layers of difficulty, but the response has been equally vigorous: from the Israeli *PI-Enroll* app (available for free to Covid-19 trials conducted in Asia, Europe and North America) to the pre-Covid-19 *CUREiTT* US app the intention of scientists was that of speeding up the recruitment process.
By helping to find and enrol Covid-19 positive patients, these and other apps can accelerate the completion of clinical trials for new drugs and vaccines. Physiologically, the pandemic has also

[1] https://i-consentproject.eu/ (last visited 31/05/2021).
[2] L. PALAZZANI, *Consenso informato alla ricerca clinica nell'ambito della pandemia CoViD-19: tra bioetica e biodiritto,* in *Biolaw Journal – Rivista di Biodiritto*, 2020, 3, 323-335.
[3] https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies (last visited 31/05/2021) My emphasis.

pushed Big Tech companies such as Google[4]) to somehow contribute to making the use of the digital tools in our hands -especially in a situation where time is key- as efficient as possible. This commitment to the usage of our digital footprints has quickly moved into the evolution of the pandemic: restriction of movement and the introduction of contact tracing apps. We will look into those next.

2. Contact tracing apps across the globe

Plenty has been written on the ethics of contact tracing apps in the past year[5] as well as various documents have been published[6] but, due to space limits, this work will be only tangent to the central concerns highlighted in those enquiries. There have been different types of contact tracing apps across the world, with very different rates of success. While in Asia (from South Korea to Singapore, Taiwan and China) the implementation of this technology was rapid and useful[7] in other parts of the globe such as the Old Continent, the various national apps provided to the population was not successful at all.

This result was due to a number of variables spanning from the technical realm (low levels of digital literacy are widespread in Southern Europe for instance) to a cultural realm – especially in Western liberal democracies, the idea of having a too intrusive State minding our business was subject to a lot of scepticism[8].

Examples such as that of Singapore -where the Government passed on the data collected by the *TraceTogether* app to the police- has come to prove that such prejudice might have been well posed in many instances. These concerns became even more pressing when the data are delegated to a private company that could "misuse" them. After all, while a police department could be using our data to enforce law (even if at times unlawfully), what exactly is the "misuse" that a private company such as Amazon[9], that has profit as a mission, could apply to our data? One of the most immediate

[4] Fierce Biotech, https://www.fiercebiotech.com/medtech/google-launches-virtual-medical-research-app-starting-studies-flu-and-covid-19 (last visited 31/05/2021).

[5] R. RANISCH, N. NIJSINGH, A. BALLANTYNE, ET AL. *Digital contact tracing and exposure notification: ethical guidance for trustworthy pandemic management*, in *Ethics Inf Technol*, 2020 https://doi.org/10.1007/s10676-020-09566-8 (last visited 31/05/2021); R. KLAR, D. LANZERATH, *The ethics of COVID-19 tracking apps – challenges and voluntariness*, in *Research Ethics*, 16(3-4), 2020, 1-9; M. KLENK, H. DUIJF, *Ethics of digital contact tracing and COVID-19: who is (not) free to go?*, in *Ethics Inf Technol*, 2020 https://doi.org/10.1007/s10676-020-09544-0; A. DUBOV, S. SHOPTAWB, *The Value and Ethics of Using Technology to Contain the COVID-19 Epidemic*, in *The American Journal of Bioethics*, 20(7), 2020, W7-W11.

[6] Austrian Bioethics Commission https://www.bundeskanzleramt.gv.at/dam/jcr:ef931182-2a1f-4d8f-aebc-72557b9f2438/Covid_ContactTracing_en.pdf (last visited 31/05/2021); The Nuffield Council on Bioethics https://www.nuffieldbioethics.org/news/guide-to-the-ethics-of-surveillance-and-quarantine-for-novel-coronavirus (last visited 31/05/2021).

[7] Y. HUANG, M. SUN, Y. SUI, *How Digital Contact Tracing Slowed Covid-19 in East Asia*, in *Harvard Business Review*, April 15 2020 https://hbr.org/2020/04/how-digital-contact-tracing-slowed-covid-19-in-east-asia (last visited 31/05/2021).

[8] W. JONKER, *Covid-19 - why didn't Europe's tracing apps work?*, in *EUObserver*, 5 February 2021 https://euobserver.com/opinion/150813 (last visited 31/05/2021).

[9] J. TAYLOR, *Questions remain over whether data collected by Covidsafe app could be accessed by US law enforcement*, in *The Guardian*, 14 May 2020 https://www.theguardian.com/law/2020/may/14/questions-remain-

issue is that of the jurisdiction of these data, but many other ethical and political concerns are surely to be taken into account – not last our behavioural habits.
Hence, aside from crucial questions such as: "Should the apps in question should be mandatory to download and use or not?" "Where will the data be stored and by who?" "Will or should a refusal to download the app automatically result in a limitation of our freedom of movement?" the intention of this paper is to make more evident the threats that might arise from the discoveries in neurosciences and their implementation by private actors (and their extensions through apps) in this pandemic. With this questioning spirit in mind, we shall move our analysis to the way behavioural analysis is more intertwined with technology next.

3. Behaviour and private companies

Scientific breakthroughs have been always thrilling our society. Nowadays, we might be facing a new stage of technological development and its impact can be compared with the Industrial Revolution of the past centuries[10]. Disruptive innovations of this technological transformation, inventions and other advances of science are not only expanding our degree of knowledge, but also provide with an opportunity to enhance mental and physical capabilities we own.
One of the most promising and fast-growing branches of the tech advances is Cognitive Technology (CT). CT or cognition-related technology is a term covering wide subset of technologies that assist, augment or simulate cognitive processes or that can be used to achieve some cognitive aims[11]. It includes two major sub-groups: neurotechnologies and Artificial Intelligent (AI) systems. The former is the set of tools that reveals human nervous system and allows to monitor and assist natural cognitive processes through the neural connections. The latter are any computer systems that are taught to mimic human intellectual patterns. It can be anything from planning and reasoning to voice and image processing as well as the interaction with the objects in a physical space. The difference between these types of the cognitive technologies is that neurotechnologies are mostly used to interact or influence "internal information processing systems", whereas AI is referred to the "external processing systems" and use external cognitive resources for supporting or enhancing human intellectual functioning.
This work wants to examine the ways current neurotechnologies are implemented into such field of human behaviour studies as marketing. By looking into which tools and methods have been already used and can be theoretically applied in the future, we will hopefully come back to the discussion on contact tracing apps with more ethical awareness regarding the potential threats of neuro and digital technologies' usage in marketing. Including of course, the dynamics currently in place in the midst of the Covid-19 pandemic.
Past decades have been marked by an extreme growth in consumption. Since shopping has switched from merely purchasing essentials to the constant evaluation of price-quality-design-ratio of all those

over-whether-data-collected-by-covidsafe-app-could-be-accessed-by-us-law-enforcement (last visited 31/05/2021).
[10] L. FLORIDI, *The Fourth Revolution: How the Infosphere is Reshaping Human Reality*, Oxford, 2014.
[11] M. IENCA, E. VAYENA, *Direct-to-Consumer Neurotechnology: What Is It and What Is It for?*, in *AJOB Neuroscience*, 10(4), 2019, 149-151.

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billions of goods and services offered to us every day, the necessity to understand what drives consumers' behaviour has become vital and urgent for producers. Marketing is a field of study that is trying to cope with this difficult question: "how does consumer's brain work?".
However, the more supply is there, the higher the complexity of the decision-making process becomes - and more efforts market researchers have to put into their studies. Once the "technological revolution" we are facing now has made it possible to glimpse into the black box navigating consumers through their shopping path, academics and self-labelled companies promptly started using the advances in neurosciences that offered powerful insights into the human brain's responses to marketing stimuli. Synergy of marketing research and neurosciences has laid the path to the development of neuromarketing.
The goals of neuromarketing are to observe objective information of the inner processes in consumers' brains that reflect their preferences and behaviour. Such research includes the use of neurotechnological applications and allow to conduct in-moment measures of the brain and body activity while making purchase decision, watching advertisement, and participating in other consumption-related processes. Neuromarketing tools' specification allows to target different experiments to the question of interest.
The most common brain-based methods are functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). fMRI helps to measure blood oxygen level dependent (BOLD) and can produce data about the neural processes that can occur depending on a different consumption experience.
For instance, recent studies conducted with fMRI showed that people are more likely to buy a product if the price was viewed first. BOLD signal that appears in the part of the brain that controls decision-making processes has been detected immediately after a purchase was made in the case where the price was shown first. On the contrary, if a person was not able to evaluate price before looking at the product BOLD signal was not marked. This discovery can affect the principles of merchandising as once people see the price and then a product itself, the assessment of the good is held with the price worthiness prevailing over the quality's estimation.
Another example is a study ran at Harvard University. It was stated that fans of a TV show "South Park" experienced changes of the BOLD signal listening to the intro music, comparing to the nonfans whose brain activity in the same area remained unchanged. Particularly this reaction was seen in the part controlling reward processing. This means that fans of the "South Park" are more vulnerable as a target group as they may be pushed towards purchasing goods or services on a subconscious level if they hear favourite music during shopping.

4. Predicting or designing?

EEG can measure arousal and even directly predict consumer behaviour even before the actual decision is made. Electrical activity of the brain that is tracked by sensors attached to the head can be highly representative when the preferences or the immediate reactions have to be observed. For example, during the experiment a focus-group was shown a trailer of an unreleased movie and the outcome has indicated that data on the participants' brain activity was correlated with the results of

a U.S. Box office for this movie after it was offered in the cinema. Similar results were stated by the research on the correlation of brain activity and future success of a particular song. Brain activity of those participants who had listened to the songs was found to be a significant predictor of the song's success three years later, whereas the survey responds of the same members were negatively correlated with the actual sales[12].

These techniques (fMRI and EEG) allow to predict decisions of a broad part of audience based on the observations of the smaller sample of participants. Along with the brain-centred methods neuromarketing applies biometrics as a measurement of a physiological responses which often can supplement each other. Eye-tracking points where the participants of the study fixated their attention or how long they were gazing at the given material. Moreover, consumers pupils' can indicate a certain extent of arousal or their interest in the product, as well as the level of hormones can reflect one's risk preferences or predict a decision. Even skin conductance observed by hand sweating can serve as an indicator of a potential customer's reaction. Neuromarketing can go beyond solely measurement and in case of a lab-conducted experiment researchers can test how direct actions affect brain or physiological activity. One of such in-lab research showed that if participants consume particular protein shake the level of serotonin in their brains, neurotransmitters that are crucial for the mood formation, can significantly decrease.

5. Stimulating the brain while ensuring informed consent

Another technique impacting natural functioning is transcranial magnetic stimulation (TMS). This method allows to brake or enhance local brain function. Magnetic fields can incapacitate one of the brain's areas, therefore reducing person's ability to engage this "knocked out" part. After researchers switch off brain region controlling certain processes, changes in a participant's behaviour can be observed. One of the discovered consequences of the TMS effect is the decreased consumer value for food. Participants of the experiment had to starve for 3 hours and then were asked to set prices for some usual products. Two groups, one that was influenced by TMS and the other that was not, showed different results. Non-stimulated people priced the food by 65% higher than those who were affected by the stimulation[13]. All these results prove that some approaches that not only "measure" consumers' reactions and behaviour but also affect them in a different way can make it possible to deplete of specific physiological reactions. Aggregation of biometrics and brain-activity measurements can allow establishing causal relationships that in the future may be used as a guidance for marketers how to build their campaigns or for producers to be precise in the product promotion as they will be sure in the effects followed by the consumption of their goods. This can lead to the significant increase in consumption which is already one of the debating issues nowadays. It seems clear that neuromarketing generates undeniable advantages over usual marketing methods and tools in terms of better prediction of success, suitability and personalization of goods and

[12] S.J. STANTON, W. SINNOTT-ARMSTRONG, S.A. HUETTEL, *Neuromarketing: Ethical Implications of its Use and Potential Misuse*, in *Journal of Business Ethics*, 144(4), 2016, 799-811.

[13] M.C. CAMUS, N. HALELAMIEN, H. PLASSMANN, ET AL., *Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex decreases valuations during food choices*, in *European Journal of Neuroscience*, 30, 2009, 1980-1988.

services. New data can make it possible to segment market in a more comprehensive way altering brain differences, instead of demographics or psychographics. However, for all the benefits both producers and consumers can take from the deepen understanding of the brain functioning it is crucial to have systematic and extensive data collection processes – research and experiments. This requires people to submit their informed consent after being explained all the procedure and the steps they will go through participating in one of these processes.

The most common issue with the clinical research is raised because it is hard to evaluate if a person is able to understand all the phases and potential risks of the research or not. Meanwhile, ethical concerns about the submitted consents in neuromarketing can slightly differ. It might be so because future participants cannot know beforehand all the details of the experiments – whether it is persuasive techniques or brain tricks that will be used, unawareness is often the initial premise and a necessary aspect for the representative results. Subsequently, if the tested methods of neuromarketing will be implemented as the regular means of persuading customers, people may also be not aware of undergoing any extraneous effects. To address this worry, in 2019 the Neuromarketing Science and Business Association established an ethical code that states that neuromarketing vendors have to provide those who actively consent to research participation with the explanation of the stages of the process and the used tools, intentions of the study and their right to withdraw at any time, as well as the assurance of the personal data protection and easy access for participants to the contents of the regulations.

Moreover, ongoing studies should not discredit the profession and the field of neuromarketing research, back all analysis and results provided to the clients by a solid scientific ground and disclose protocols in case of incidental findings during tests applying fMRI data capture. Nonetheless, this code is a first step on the way to the ethical neuromarketing implementation and there is still high variability in benefits to participants and neuromarketing firms across different protocols used in the industry[14]. Other ethical concerns are raising due to the passive data acquisition that is frequently occurring nowadays (especially in the present circumstances of the Covid-19 outbreak and ubiquitous placement of the protective technologies).

6. Determining who buys what?

Thermal cameras, video-based face recognition or emotion detection – these technologies are widely spreading, especially in contexts where authorities see public safety as superior to privacy or individual freedoms. For instance, the Chinese government is using video-based face recognition to identify and test citizens who have been previously accused of the drug possession[15]. Another type of technologies - emotion detection - can describe facial expressions, which then can be analysed by AI and be assessed to one of the 7 universal groups (anger, contempt, disgust, enjoyment, fear,

[14] K.R. CLARK, *A field with a view: Ethical considerations for the fields of consumer neuroscience and neuromarketing. Ethical Dimensions of Commercial and DIY Neurotechnologies Developments*, in *Neuroethics and Bioethics*, 2020, 23-61.

[15] J. GOLDKORN, *Drug users nabbed by facial recognition system at beer festival—China's latest top news*, in *SupChina*, September 1 2017 https://supchina.com/2017/09/01/drug-users-nabbed-facial-recognitionsystem-beer-festival-chinas-latest-top-news/ (last visited 31/05/2021).

sadness, surprise)[16]. The spin-offs of the ethical concerns related to such invasive use of technology cannot be analysed more in details here.

Currently, due to the active development of the Web and social media usage, where content is created and shared based on an open-access concept (Facebook, Instagram, Twitter, Snapchat and so on) the application of CT has boomed. It has become the standard that for-profit companies can play on our emotions, having access to these media-based technologies and targeting us according to the mood we are in (generating at times dependence from this very toxic stimulating system). Shoshana Zuboff has recently shed light[17] on how surveillance has changed in the internet era. Not only we can be screened by cameras in the streets, but our digital footprint can feed algorithms and machines with our data, generating more personalized and precise marketing approaches. Messages we text, photos and videos that are post or sent – all these can trigger an immediate offer from those who are able to process our biological data and classify as an angry or happy potential customer. Taking as an example the dystopian movie *Minority Report* where advertisements in the shopping centre were adopting according to whom technologies were recognizing and which emotions and desires a person possessed. This idea of "bioscanning" from the 2002 sci-fi movie is turning into 2021 everyday reality -with some shopping malls already capable to tailor the ads on a specific customer. Unprotected personal information that can flow from one company to another while being processed multiple times on the way makes it possible to apply neuromarketing tools to a large number of people even without direct brain scanning. For instance, after our own faces and emotions are identified and analysed by modern technologies and algorithms, they can be stored and recovered once new technologies are available – so to have a new special type of advertisements.

One of the ways companies may play with our brains could be based on the results of the research showing that people are more attracted by those who are physically resembling themselves[18] . Even political and social campaigns can undergo some conceptual changes: during the study, participants were shown two photos of unfamiliar political candidates. One of them had some artificially added elements in their physical appearance taken from the very voter or extracted from the other participants with similar looks. It was noted a very strong correlation between the preferences and the familiarity of the face chosen[19]. Tricks like this one are invisible to the users' eyes, but if potential customers or voters get personalized advertisement or political campaigns can hide subconscious leverages, it will be hard not talk about brainwashing -making it really complicated to distinguish decisions reflecting free will of a person from those that were imposed from outside.

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[16] P. EKMAN, *The argument and evidence about universals in facial expressions of emotion* in H. WAGNER, A. MANSTEAD (Eds.), *Wiley handbooks of psychophysiology. Handbook of social psychophysiology*, Chichester, 1989, 143-164.

[17] S. ZUBOFF, The Age of Surveillance Capitalism: The Fight for a Human Future at the New Frontier of Power, New York, 2019.

[18] L.M. DEBRUINE, *Resemblance to self increases the appeal of child faces to both men and women*, in *Evolution and Human Behavior*, 25, 2004, 142-154; M.I. GOBBINI, J.D. GORS, Y.O. HALCHENKO, ET AL., *Prioritized detection of personally familiar faces*, in *PLoS One*, 8(6), 2013, e66620.

[19] J.N. BAILENSON, S. IYENGAR, N. YEE, N.A. COLLINS, *Facial similarity between voters and candidates causes influence*, in *Public Opinion Quarterly*, 72(5), 2008, 935-961.

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Regarding users' protection in the digital space, GDPR is the main regulator for organizations using personal data. Privacy policy should be clearly explained and provided directly to everyone whose data can be processed while online -or at times even without even being online (e.g. being recorded by a Google car while cutting one's garden). In practice, many of the users are not able to competently agree on consent asked to them or clearly understand the terms and conditions they encounter when accessing a website or an app, because these documents are often extremely long, at times unclear and require a certain digital literacy. That is why, in theory, sites and companies are obtaining users' informed consent on the Internet, whereas, in practice, once a person is asked to explain what exactly he or she allows to do with the personal information that was allowed to be aggregated during the search – only few would be able to respond in the way their consent can be counted.

We make our everyday decisions basing on conscious and unconscious processes instantly going on inside the brain. This black box is driving us through millions of choices we have to take every day. The rise of purchasing power of a large part of the population has boosted up the demand which in turn has affected the supply side. We often hear the phrase "we have an opportunity to buy anything we want from anyone we want". However, the limits of our will are becoming blurrier. Which "part" of us is really *being* determined? Is it consciousness that gives a right answer to the question on whether it is worth doing something or we are driven by one of those neural impulses inside the brain? The development of CT has lifted the veil of some of the brain's secrets. It is beyond the scope of this work to engage with a philosophical discussion on determinism, but in this context suffice to say that marketers are eager to implement CT into their field and lay the path for the neuromarketing progress. It has become clearer that subconscious plays a significant role in the decision-making processes.

EEG, fMRI, biometrics' trackers and stimulators have made it possible to understand and even affect brain processes - regulating consumer behavioural patterns inside this subconscious layer. Digital technologies (and apps) have taken and are taking advantage of these findings in marketing - especially when connected to companies that are, after all, in the game for profit. From what highlighted here, it seems crucial to raise the level of consumers' awareness about methods and means that are used and can be used in the future by neuro and digital marketers -because this could quite directly affect their willingness to give consent (or not) to the use of a certain app or the extraction and (future) storage of their data.

If we combine what just highlighted with the increase use of "data extractors" such as Palantir, it should become even more apparent that we are at risk of being pushed towards a certain *commercial direction* without even knowing about it

On its website, Palantir -a gigantic private company on which secret services and powerful sovereign states, but also commercial companies, have increasingly relied upon in the last decade- states: "we build software that lets organizations integrate their data, their decisions, and their operations into one platform. Our software empowers entire organizations to answer complex questions quickly by bringing the *right* data to the people who *need* it."[20]

[20] https://www.palantir.com/ (last visited 31/05/2021).

What is the right data though? And who needs what? Palantir continues by explaining how they preserve our [mental?] privacy by affirming: "from our roots in counterterrorism to our current work spanning the public, private, and non-profit sectors, we've delivered software that incorporates principles of privacy by design." Yet, their immense power might derive precisely from being able to gather data from the loopholes that do not define an infringement of one's privacy extracting data from an app, neural activity or website only because the design is such that our privacy is not "encrypted". That is far from a satisfactory answer to the ethical concerned raised by these technologies, and the Covid-19 pandemic might have helped us realize how murky some dynamics really are.

7. Concluding remarks

The Covid-19 pandemic has brought forward many unforeseen scenarios and many of those have been directly related to the unprecedented level of technological advancement that is currently in our hands. Especially in the beginning of the pandemic, one of the most evident implementations of digital technology aimed at fighting against Covid-19 have been contact tracing apps and, to a lesser extent, other apps related to the pandemic (such as those helping recruiting people for clinical trials). Many countries have successfully used (in more or less liberal terms) these apps, whereas Western realities have struggled much more to implement them in a way that produced an impact. While the ethical debate concerning apps developed to contrast the pandemic has mostly focused on how the State should protect its citizens from the dark side of this intrusive technologies, this paper has addressed the commercial dynamics behind the private, non-state control usage of the technology - and the pandemic. By focusing on the developments of neuromarketing, business strategies increasingly connected with the exploitation of our data and the unclarity that still is connected with some private project -even more so than with already controversial results run by the State such *TraceTogether*- the suggestion here is to enlarge our scanning of the ethical soundness of certain apps also to the private sector.

As we are entering another emotionally charged phase of debates over the use of apps connected to Covid-19, it is important to increase -and not jeopardize further- trust in authorities. It is the only way in which global tracing apps (such as those called by some "vaccine passport apps")[21] could have a chance to not exacerbate further some of the concerns already raised across the European Union when discussing other contact tracing apps[22]. If privacy is power, as Carissa Véliz convincingly argues in her recent book[23], more attention should be given to the use of our data by a private company in a state of emergency such as the one we are living in. Examples of private empires such as Palantir (able to provide services related to the usage of data to various countries across the globe in the form of assistance for police departments and secret services) exemplify the dominance of expertise

[21] S.M. KELLY, *Vaccine passport apps could help us return to normal. First they need to solve the trust problem*, in *CNN Business*, 29 March 2021 https://edition.cnn.com/2021/03/29/tech/vaccine-passport-app-privacy/index.html (last visited 31/05/2021).

[22] C. GOUJARD, *Europe risks another tech tangle with vaccine passports*, In *Politico*, 13 April 2021 https://www.politico.eu/article/vaccine-passports-echo-coronavirus-app-failures/ (last visited 31/05/2021).

[23] C. VÉLIZ, *Privacy is Power*, London, 2020.

of the private sector over the public in (mis)using our data. If we feel already uncomfortable with the State knowing *too much* about us, should we not be even more concerned to give consent to a "private" app that will structurally entail a direct profit for someone (moreover, inevitably based on us in some ways)?

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Special issue

Informed consent and artificial intelligence applied to RCT and Covid-19

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ABSTRACT: Artificial intelligence (AI) tools allow to extract knowledge from big data and are increasingly used for research purposes applied to -omics, diagnostic images, complex patterns of diseases and system medicine, drug development, robotics, and other topics. The management of big data, largely made of individual clinical data, poses specific ethical challenges that must be addressed in research studies and that should be reflected in the informed consent process. Explaining the mechanisms used by AI algorithms in supporting clinical decision making may be particularly difficult because of the opacity of its process. Moreover, depending on the quality of data feeding their algorithms, AI applications may result in errors. As the General Data Protection Regulation (GDPR) includes the possibility that a patient withdraws his/her informed consent from a study, it may be challenging to update AI algorithms accordingly. On the other hand, AI tools may help support the recruitment and retention of participants in clinical trials matching eligibility criteria with individual data collected for clinical purposes in electronic health records, and improve data collection and analytics. The possibility to stream data from wearable devices offers the possibility to generate large data volumes relevant to Patient Reported Outcomes feeding AI predictive algorithms. The Covid-19 pandemic has promoted the application of digital tools and of AI in clinical trials in order to limit personal contacts. The pressure exerted by the pandemic will possibly speed up the adoption of AI solutions for clinical trials and will highlight their potential ethical implications.

KEYWORDS: Artificial intelligence, Covid-19, ethics, informed consent, randomized clinical trial

SUMMARY: 1. Introduction – 2. Applications of AI in healthcare – 3. Ethical challenges of AI – 4. The risks of AI in healthcare – 5. Emerging uses of AI in research studies – 6. The Covid-19 pandemic – 7. GDPR and AI in healthcare – 8. Shaping the informed consent for AI interventions – 9. Conclusions.

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1. Introduction

The very essence of artificial intelligence (AI) applications in health care relies on the availability of big data generated by a network of multiple stakeholders engaged in data sharing. As AI is already pervasive in our daily life in other domains, we expect that this technology will become common in healthcare as well. The impact of AI in healthcare may be enormous if we will be able to properly share the largest amount of data possible as it happened when the exponential computing power of the internet skyrocketed in the early nineties and one million computing machines were connected on the web. As health care is typically organized in silos of data, overcoming this barrier to appreciate a significant impact on population health will be a challenge with a number of ethical implications, including the informed consent process.

Many health care problems could be addressed by AI applications that may resolve several high priority issues, from drug development, to prediction of clinical severe events, to what is one of the most abused terms of the last years: precision medicine. Indeed, a deep integration of AI in healthcare processes and research is yet to come, the main barrier being the lack of interoperability of data repositories.

The Covid-19 pandemic has increased the sense of urgency to address healthcare solutions that are still unresolved. On the other hand, the pandemic has accelerated and favored the application of digital tools using AI that may be suitable to support mitigation strategies for the pandemic. For this reason, we expect that the hype of digital and AI tools will soon result in using them in routine clinical care. Nevertheless, novel AI medical interventions will require proof of safety and efficacy through clinical trials. AI is expected to become one of the many tools available to deliver preventative, diagnostic and therapeutic interventions, but contrary to traditional medical interventions, being a software. Yet, the many specificities of AI tools and their intersection with human decisions require tailored ethical strategies. All these circumstances call for a deep reflection on the ethical implications of AI in healthcare to avoid that the promises of technologies and the hope for effective novel tools to combat the pandemic will obscure the basic principles of ethics in the interest of patients. Moreover, because of their nature, AI applications in healthcare may result in ethical and legal challenges regarding responsibilities and liability. We need to focus on the specificities that informed consent has in these particular circumstances as it is the most important process through which patients make their decisions in healthcare.

2. Applications of AI in healthcare

AI techniques vary in their mechanism and deployment in healthcare. Algorithms may use machine learning (ML) or deep learning (DL), with different levels of complexity and performance. An area where AI is applied is interpretation of natural language with Natural Language Processing (NLP) techniques. Often, a combination of these technologies is applied in robotics[1].

[1] ANTHONY C. CHANG, *Intelligence-Based Medicine: Artificial Intelligence and Human Cognition in Clinical Medicine and Healthcare*, Elsevier Science, Amsterdam, 2020, pp. 534.

The potential applications of AI in healthcare are almost limitless[2] and its impact has become clear for both clinicians, health systems and patients[3]. The most exciting advances have been observed in the field of diagnostic image interpretation. It is already possible to automatically classify retinal photographs of diabetic patients and diagnose macular edema or retinopathy[4,5]. Several companies have already developed systems that are embedded into the radiologic equipment and that support the detection of cardiovascular diseases and other conditions, such as lung nodules or breast mass[6,7]. A similar progress has been observed in dermatology, where AI applications proved to be more accurate than a human observer in the detection of many types of skin lesions[8]. AI has also been successfully applied to pathology for classification of biopsies and detection of oncologic anomalies[9].
A more popular application of AI regards the interpretation of complex genetic patterns that may be associated with specific diseases[10]. Moreover, AI may help understanding the role of even more complex patterns including gene expression, protein abundance levels and methylation profiles in predicting several diseases (omics approaches), with implications in the discovery of novel biomarkers of disease[11].
AI is also helpful in predicting the prognosis of patients based on information recorded in the electronic health records (EHR). With this approach, it is possible to predict mortality, readmission and length of stay of complex patients, helping to implement appropriate countermeasures[12].

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[2] K. H. Yu, A. L. Beam, and I.S. Kohane, *Artificial Intelligence in Healthcare*, in *Nature Biomedical Engineering* 2, no. 10 (October 2018): 719–31.
[3] E. J. Topol, *High-Performance Medicine: The Convergence of Human and Artificial Intelligence*, in Nature Medicine 25, no. 1 (January 2019): 44–56.
[4] M. D. Abràmoff et al., *Improved Automated Detection of Diabetic Retinopathy on a Publicly Available Dataset Through Integration of Deep Learning*, in *Investigative Ophthalmology & Visual Science,* vol. 57, no. 13 (1 October 2016): 5200–5206.
[5] A. Grzybowski et al., *Artificial Intelligence for Diabetic Retinopathy Screening: A Review*, in *Eye* vol. 34, no. 3 (March 2020): 451–60.
[6] B. van Ginneken et al., *Off-the-Shelf Convolutional Neural Network Features for Pulmonary Nodule Detection in Computed Tomography Scans*, in *IEEE 12th International Symposium on Biomedical Imaging (ISBI)*, 2015, 286–89.
[7] R. K. Samala et al., *Mass Detection in Digital Breast Tomosynthesis: Deep Convolutional Neural Network with Transfer Learning from Mammography*, in *Medical Physics* vol. 43, no. 12 (December 2016): 6654.
[8] A. Esteva et al., *Dermatologist-Level Classification of Skin Cancer with Deep Neural Networks*, in *Nature* 542, no. 7639 (February 2017): 115–18.
[9] G. Litjens et al., *Deep Learning as a Tool for Increased Accuracy and Efficiency of Histopathological Diagnosis*, in *Scientific Reports* vol. 6, no. 1 (23 May 2016): 26286**;** B. E. Bejnordi et al., *Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women with Breast Cancer*, in *JAMA* vol. 318, no. 22 (12 December 2017): 2199–2210.
[10] D. Quang, Yifei Chen, and X. Xie, *DANN: A Deep Learning Approach for Annotating the Pathogenicity of Genetic Variants*, in *Bioinformatics* (Oxford, England) 31, no. 5 (1 March 2015): 761–63; D. Quang and Xiaohui Xie, *DanQ: A Hybrid Convolutional and Recurrent Deep Neural Network for Quantifying the Function of DNA Sequences*, in *Nucleic Acids Research* 44, no. 11 (20 June 2016): e107.
[11] N. Biswas and S. Chakrabarti, *Artificial Intelligence (AI)-Based Systems Biology Approaches in Multi-Omics Data Analysis of Cancer*, in *Frontiers in Oncology* 10 (2020): 588221.
[12] J. M. Karnuta et al., *The Value of Artificial Neural Networks for Predicting Length of Stay, Discharge Disposition, and Inpatient Costs after Anatomic and Reverse Shoulder Arthroplasty*, in *Journal of Shoulder and Elbow Surgery* 29, no. 11 (1 November 2020): 2385-94.

AI is also used to interpret continuous data streams of vital signs and other information, such as voice and movement generated by wearable devices. We started only recently to collect these data and to use them for diagnostic purposes often in complement with traditional clinical data[13].
Robotic systems, that are gradually taking place in surgery, offer another example of application of AI, taking also into consideration that it is likely that in the future robotic surgery will become autonomous[14]. Automation, however, is also found in technologies that interact with humans through natural speech. The capacity of AI to process natural language allows to develop social robots or chatbots[15] that may be used for health interventions.
Finally, a new class of therapies is becoming available, namely digital therapeutics. These therapies include as an active principle an AI software instead of a chemical or biological compound. Their application is mainly in the domain of behavioral treatments and support of adherence to pharmacological therapies[16].

3. Ethical challenges of AI

One known issue of AI interventions is the "black box" problem. Although AI systems are fed with known input data, and they generate explicit output data, the logic behind an AI algorithm may be opaque. This makes it difficult to understand, explain how, and the reason why an algorithm arrived at a specific result[17]. Indeed, AI algorithms do not apply synthetic rules, but they are rather trained on examples that may be difficult to reduce to simple logic.
According to the latest European Commission guidelines, trustworthy AI should be "(1) lawful, respecting all applicable laws and regulations; (2) ethical, respecting ethical principles and values; (3) robust, both from a technical perspective while taking into account its social environment"[18]. Moreover, both the Food and Drug Administration (FDA) and the European Commission consider transparency a fundamental requirement for AI systems in healthcare[19]. Transparency is intended as

[13] A.C. CHANG, *Intelligence-Based Medicine: Artificial Intelligence and Human Cognition in Clinical Medicine and Healthcare*, Elsevier Science, Amsterdam, 2020, pp. 534.
[14] A. SHADEMAN ET AL., *Supervised Autonomous Robotic Soft Tissue Surgery,* in *Science Translational Medicine 8, no. 337 (4 May 2016): 337ra64*; R. ELEK ET AL., *Recent Trends in Automating Robotic Surgery,* in *2016 IEEE 20th Jubilee International Conference on Intelligent Engineering Systems (INES), 2016, 27–32.*
[15] A.C. CHANG, *Intelligence-Based Medicine: Artificial Intelligence and Human Cognition in Clinical Medicine and Healthcare*.
[16] O. SVERDLOV ET AL., *Digital Therapeutics: An Integral Component of Digital Innovation in Drug Development,* in *Clinical Pharmacology and Therapeutics* 104, no. 1 (July 2018): 72–80.
[17] M. CARABANTES, *Black-Box Artificial Intelligence: An Epistemological and Critical Analysis,* in *AI & SOCIETY 35* (1 June 2020).
[18] HIGH-LEVEL EXPERT GROUP ON ARTIFICIAL INTELLIGENCE, *Ethics Guidelines for Trustworthy AI. Shaping Europe's Digital Future*, April 2018, available at https://digital-strategy.ec.europa.eu/en/library/ethics-guidelines-trustworthy-ai (last accessed May 10th, 2021); EUROPEAN COMMISSION, *Proposal for a Regulation of the European Parliament and of the Council Laying Down Harmonised Rules on Artificial Intelligence (Artificial Intelligence Act) and amending certain union legislative acts*, 2021, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELLAR%3Ae0649735-a372-11eb-9585-01aa75ed71a1 (last accessed May 10th, 2021).
[19] U.S. FOOD AND DRUG ADMINISTRATION, *Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)-Discussion Paper and Request for Feedback,* 2019, https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-

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clarity of the AI systems themselves, of the kind of data used and the processes they follow to reach a result, and should apply to the output and to the functions of the software and its modifications over time to create trust among users[20].

Explainability can be considered as "a characteristic of an AI-driven system allowing a person to reconstruct why a certain AI came up with the presented predictions"[21]. While traditional algorithms are characterized by an inherent explainability[22], in DL algorithms such as artificial neural networks, explainability is not inherent to the system, but is approximated, due to the complex characteristics of the system itself. When it comes to medical AI-driven procedures, such as those implied in supporting clinical decision, lack of explainability may have important legal and ethical implications[23].

It may happen that AI algorithms are biased because of a non-sufficiently diverse training set or missing data, leading to disparities when applied to healthcare. For example, individuals from disadvantaged communities may access multiple institutions (i.e. less likelihood to find patients who have data in different EHRs), or data about race/ethnicity, socioeconomic status may be missing in the EHR leading to underrepresentation and bias toward these communities[24]. Data availability, data collection from minorities and specification of the population for which the algorithms is developed, are examples of standards and measures that could address some of these issues[25].

Big data needed for artificial intelligence applications in healthcare may fall under the control of various organizations, which may share these data for health research. Moreover, especially when data is collected from multiple data sources, identification or re-identification, which is technically feasible, may be useful for AI to recognize and exploit associations among data sources. If we consider the example of research in genomics or in multiple -omics, where AI techniques are largely applied, it should be considered that genetic information carries data relevant to relatives and may be re-identified[26].

Machine-Learning-Discussion-Paper.pdf (last accessed May 10th, 2021); EUROPEAN COMMISSION, *White Paper on Artificial Intelligence: A European Approach to Excellence and Trust,* February 2020*,* https://ec.europa.eu/info/sites/info/files/commission-white-paper-artificial-intelligence-feb2020_en.pdf (last accessed May 10th, 2021).

[20] H. FELZMANN ET AL., *Towards Transparency by Design for Artificial Intelligence,* in *Science and Engineering Ethics* vol. 26, no. 6 (December 2020): 3333–61.

[21] J. AMANN ET AL., *Explainability for Artificial Intelligence in Healthcare: A Multidisciplinary Perspective,* in *BMC Medical Informatics and Decision Making* vol. 20, no. 1 (30 November 2020): 310.

[22] C. RUDIN, *Stop Explaining Black Box Machine Learning Models for High Stakes Decisions and Use Interpretable Models Instead,* in *Nature Machine Intelligence* vol. 1, no. 5 (May 2019): 206–15.

[23] J. AMANN ET AL., *Explainability for Artificial Intelligence in Healthcare: A Multidisciplinary Perspective,* in *BMC Medical Informatics and Decision Making* vol. 20, no. 1 (30 November 2020): 310.

[24] M. A. GIANFRANCESCO ET AL., *Potential Biases in Machine Learning Algorithms Using Electronic Health Record Data,* in *JAMA Internal Medicine* vol. 178, no. 11 (1 November 2018): 1544–47.

[25] S. GERKE, T. MINSSEN, AND G. COHEN, *Ethical and Legal Challenges of Artificial Intelligence-Driven Healthcare,* in *Artificial Intelligence in Healthcare,* 2020, 295–336.

[26] J. S. WINTER AND E. DAVIDSON*, Governance of Artificial Intelligence and Personal Health Information, Digital Policy, Regulation and Governance* 21, no. 3 (1 January 2019): 280–90.

4. The risks of AI in healthcare

AI interventions should be progressively adapted to and incorporated into clinical research, but they require an adaptation of study designs developed for drugs. Robust clinical trials to understand the potential benefits and risks of an algorithm are needed[27]. Moreover, risks that are specific of AI should be considered in the informed consent process in clinical studies involving this intervention. In particular, AI systems may come across specific potential risks such as error, bias, cyberattacks and re-identification of anonymous data.

As it may happen with a navigation system that fails to indicate the right way during a car trip, an AI algorithm may incur in error for various reasons, including the possibility that the AI system has not been properly trained with cases similar to a specific situation. Such a situation may cause severe events if AI is applied in high-risk settings like intensive care units. Although promising, these applications still need to be studied to reach the highest level of confidence in patients with high risk of complications and death. It must be noted that not only AI systems may be not appropriately trained, but also AI is still not able to adequately recognize a causation compared to a correlation, and this could lead to recommendations that do not correspond to the actual patient's background and needs[28].

Ideally, AI systems should be fed with the largest amount of data available. Still, data available for training an algorithm may be biased and may not represent all the individuals to whom AI algorithms will be applied. Bias could derive from a non-heterogeneous training data set[29], missing data and patients not identified by algorithms, small sample size and underestimation, misclassification and measurement errors[30]. Although humans are subject to bias as well, these potential problems should be taken into account when developing algorithms for clinical support and medical decision, and preventive measures should be adopted[31].

Cyberattacks are becoming a real threat for the health sector[32] and their frequency is increasing, especially during critical situations, such as a pandemic[33]. A particularly dangerous threat is represented by "input attacks", consisting in manipulating the data used by the AI system in order to alter the output of the system[34]. For example, a MRI image can be modified so that the AI will detect

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[27] E.J. TOPOL, *Welcoming New Guidelines for AI Clinical Research*, in *Nature Medicine* vol. 26, no. 9 (September 2020): 1318–20, https://doi.org/10.1038/s41591-020-1042-x.

[28] M. KIENER, *Artificial Intelligence in Medicine and the Disclosure of Risks,* in *AI & Society,* 22 October 2020, 1–9.

[29] R.B. PARIKH, S. TEEPLE, A. S. NAVATHE, *Addressing Bias in Artificial Intelligence in Health Care,* in *JAMA*, 22 November 2019.

[30] M.A. GIANFRANCESCO ET AL., *Potential Biases in Machine Learning Algorithms Using Electronic Health Record Data,* in *JAMA Internal Medicine* vol. 178, no. 11 (1 November 2018): 1544–47.

[31] M.A. GIANFRANCESCO ET AL., *Potential Biases in Machine Learning Algorithms Using Electronic Health Record Data*.

[32] S.T. ARGAW ET AL., *The State of Research on Cyberattacks against Hospitals and Available Best Practice Recommendations: A Scoping Review, BMC Medical Informatics and Decision Making* 19, no. 1 (11 January 2019): 10.

[33] H. S. LALLIE ET AL., *Cyber Security in the Age of COVID-19: A Timeline and Analysis of Cyber-Crime and Cyber-Attacks during the Pandemic, ArXiv E-Prints* (1 June 2020), arXiv:2006.11929, available at https://arxiv.org/abs/2006.11929 (last accessed May 10th, 2021).

[34] M. COMITER, *Attacking Artificial Intelligence. Paper, Harvard Kennedy School, Belfer Center for Science and International Affairs, August* 2019, available at https://www.belfercenter.org/sites/default/files/2019-08/AttackingAI/AttackingAI.pdf (last accessed May 10th, 2021).

a false malignant diagnosis. These attacks do not interfere with the AI algorithms themselves, hence they are difficult to detect. Moreover, they should be considered as "inherent" risks in AI-based medical procedures[35].

Privacy and confidentiality are two of the fundamental principles in managing personal data. Patients have the right of control and decide on their health information and physicians have the duty to guarantee privacy[36]. Even if data are anonymized the risk of re-identification in particular circumstances, i.e. getting the patient's identity by matching and combining different data, is real and has to be taken into account[37].

5. Emerging uses of AI in research studies

AI may significantly improve the efficiency of clinical trials in all phases, from early design, to recruitment, conduction of the study, and reporting activities. AI may help to improve patient selection during recruitment, to reduce heterogeneity and even to select patients with a higher probability to have the outcome under study and more likely to respond to a treatment[38]. It has been suggested that NLP techniques may be used to analyze data from EHRs and social networks to balance the underrepresentation of certain groups such as black people or older adults[39]. Moreover, AI and other digital tools have been indicated as potential solutions for running decentralized or virtual/hybrid clinical trials. These kinds of trials are characterized by a limited in person interaction between trial participants and the investigation site. Digital technologies, including NLP, wearable devices and biosensors, can ideally support the tasks of usual clinical trials with significant resource savings. Decentralized trials, moreover, allow patients to report their outcomes autonomously, which has implications for data quality and for the success of clinical studies. This possibility has raised interest in the use of digital markers that are mostly linked to personal behaviors but that can be collected through simple devices such as a smartphone[40].

Digitized clinical trials should apply appropriate privacy, safety, and regulatory measures. First, the enormous amount of data exchanges require security measures to prevent data breaches. This observation is relevant to cybersecurity, which is a component of medical device certification[41]. Blockchain has been indicated as an helpful technology to prevent breaches of databases containing sensitive information[42]. A blockchain is a digital transaction archive, which guarantees immutability and privacy of transactions through duplication over the entire computer network. Its application is

[35] M. KIENER, *Artificial Intelligence in Medicine and the Disclosure of Risks,* in *AI & Society,* 22 October 2020, 1–9.
[36] P. BALTHAZAR ET AL., *Protecting Your Patients' Interests in the Era of Big Data, Artificial Intelligence, and Predictive Analytics,* in *Journal of the American College of Radiology: JACR* vol. 15, no. 3 Pt B (March 2018): 580–86.
[37] S. CHOUDHURY ET AL., *Big Data, Open Science and the Brain: Lessons Learned from Genomics,* in *Frontiers in Human Neuroscience* vol. 8 (2014): 239.
[38] S. HARRER ET AL., *Artificial Intelligence for Clinical Trial Design,* in *Trends in Pharmacological Sciences* vol. 40, no. 8 (August 2019): 577–91.
[39] O.T. INAN ET AL., *Digitizing Clinical Trials,* in *NPJ Digital Medicine* vol. 3, 101 (2020).
[40] O.T. INAN ET AL., *Digitizing Clinical Trials,* cit.
[41] O.T. INAN ET AL., *Digitizing Clinical Trials*, cit.
[42] P.V. KAKARLAPUDI AND Q. H. MAHMOUD, *A Systematic Review of Blockchain for Consent Management,* in *Healthcare* (Basel, Switzerland) 9, no. 2 (1 February 2021).

particularly interesting because it allows patients to manage their personal data with smart contracts[43]. Blockchain allows different permission levels for different users when accessing personal data. This means that a patient may authorize a medical doctor to access her sensitive data but only a fraction of them may be available for a medical researcher. The same flexibility may be applicable to Internet of Things (IoT) devices where a patient may decide to revoke her decision at any time. Application of blockchain to AI interventions paves the way to future development of research based on data sharing which will require consideration in the ethical dimension and the informed consent process. Indeed, blockchain has implications in data authentication, storage, and privacy, which should be properly reflected in the informed consent process[44].

6. The Covid-19 pandemic

The Covid-19 pandemic has represented a stimulus in the implementation of electronic consent in clinical research. Several existing digital strategies have been reinforced to cope with difficulties in enrollment, including re-consent due to travel restrictions, and other measures that favored the transition from traditional to virtual clinical trials. The FDA, for example, has developed a platform allowing investigators to replace traditional consent with an electronic version[45]. Similarly, the health authorities in Singapore issued recommendations supporting the use of eConsent[46]. Finally, the European Medicine Agency has proposed alternatives to the traditional in person process for clinical trials, when participants are unable to consent in person, including electronic alternatives[47]. On the other hand, the pandemic emergency has limited research activities and development of AI tools because they cannot be trained on large numbers of observations and from homogeneous populations, resulting in bias[48].

Indeed, the Covid-19 pandemic has stimulated the development of a number of tools based on AI to monitor, model, control, mitigate, diagnose and treat the SARS COV2 infection. Among those directly inherent to patients, attempts have been made to develop algorithms for correctly interpreting diagnostic images. The results of these efforts were very good, but with little practical application as diagnostic images may be normal in early phases of infection, and very easy to interpret once pneumonia is established. Simple AI based models have been proposed to develop efficient strategies for viral diagnostic tests. AI has also been used for drug discovery for Covid-19, which led to significant

[43] Y. ZHUANG ET AL., *Applying Blockchain Technology to Enhance Clinical Trial Recruitment,* in *AMIA Annual Symposium Proceedings* 2019 (4 March 2020): 1276–85.

[44] P. V. KAKARLAPUDI AND Q. H. MAHMOUD, *A Systematic Review of Blockchain for Consent Management*.

[45] U.S. FOOD AND DRUG ADMINISTRATION, *COVID MyStudies Application (App),* 29 May 2020, https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app (last accessed May 10th, 2021).

[46] SINGAPORE HEALTH SCIENCE AUTHORITY, *Guidance on the Conduct of Clinical Trials in Relation to the COVID-19 Situation,* 29 July 2020, https://www.hsa.gov.sg/docs/default-source/hprg-io-ctb/hsa_ctb_covid-19_guidance_for_clinical_trials_29jul2020.pdf (last accessed May 10th, 2021).

[47] EUROPEAN MEDICINES AGENCY (EMA), *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic,* 4 February 2021, https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf (last accessed May 10th, 2021).

[48] M. KIENER, *Artificial Intelligence in Medicine and the Disclosure of Risks,* in *AI & Society,* 22 October 2020, 1–9.

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hypotheses for candidate therapies[49]. These examples underline how important is to balance the urgency to discover new solutions for an emerging disease with the ethical implications.

7. GDPR and AI in healthcare

The General Data Protection Regulation (GDPR) is currently the strongest data protection regulation in the world[50]. The GDPR aims at preventing unconsented and secondary uses of personal data, but also reduces administrative formalities before accessing and using health data. Among the rights highlighted by the GDPR, "Non-Discrimination Right", the "Right to Explanation", and the "Right to Be Forgotten" are included[51]. A biased algorithm applied to healthcare can result in discriminatory decision-making. As discrimination is forbidden according to EU law, even when it is indirect, there is a need to prevent that as underlined in article 22 of the GDPR[52,53]. For what concerns the "Right to be Forgotten", as explained in the article 17 of the GDPR, a subject has the right to have her personal data eliminated and no longer available and processed. This principle is not easy to apply to AI, because data deletion in AI contexts is complex and algorithms do not forget the way humans do[54]. Therefore, looking for potential solutions to protect this right in a way doable for machine learning environments is one of the challenges of AI in healthcare.

Another rule that is included in GDPR is that de-identification, a technique to remove personal data leading to identification of an individual, is not considered sufficient to prevent re-identification. Therefore, de-identified data are still considered protected personal data, while only anonymous data are excluded from its application. According to GDPR, anonymous data is "information which does not relate to an identified or identifiable natural person or to personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable". Inadequate anonymization could be applied due to several misunderstandings[55].

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[49] A. C. Chang, *Artificial Intelligence and COVID-19: Present State and Future Vision,* in *Intelligence-based medicine* 3, 100012. https://doi.org/10.1016/j.ibmed.2020.10001.

[50] European Parliament, *Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on the Protection of Natural Persons with Regard to the Processing of Personal Data and on the Free Movement of Such Data, and Repealing Directive 95/46/EC (General Data Protection Regulation),* available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN (last accessed May 10th, 2021).

[51] J. S. Winter and E. Davidson, *Governance of Artificial Intelligence and Personal Health Information, Digital Policy, Regulation and Governance* 21, no. 3 (1 January 2019): 280–90.

[52] European Union Agency for Fundamental Rights, *#BigData: Discrimination in Data-Supported Decision Making, Focus Paper,* 28 May 2018, available at https://fra.europa.eu/en/publication/2018/bigdata-discrimination-data-supported-decision-making (last accessed May 10th, 2021).

[53] European Parliament, *Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation*).

[54] E. F. Villaronga, P. Kieseberg, T. Li, *Humans Forget, Machines Remember: Artificial Intelligence and the Right to Be Forgotten,* in *Computer Law & Security Review* vol. 34, no. 2 (1 April 2018): 304–13, https://doi.org/10.1016/j.clsr.2017.08.007.

[55] Agencia Española de Protección Datos (AEPD), European Data Protection Supervisor (EDPS), *AEPD-EDPS Joint Paper on 10 Misunderstandings Related to Anonymisation,* 27 April 2021, https://edps.europa.eu/data-protection/our-work/publications/papers/aepd-edps-joint-paper-10-misunderstandings-related_en (last accessed May 10th, 2021).

The GDPR also uses a clear definition of the informed consent that should be "freely given, specific, informed and unambiguous", that it should be explicit and informed and that "silence, pre-ticked boxes or inactivity should not therefore constitute consent". This information must be taken into account when considering the use of electronic consent for studies on AI interventions. Regarding the management of sensitive data, the GDPR states that data processing should be limited to predefined purposes although secondary use of data is allowed for scientific research purposes. As AI algorithms need large amounts of data to be trained, it is likely that this process will rely on the reuse of personal data collected for other purposes, and this may be a limitation in their development[56]. One of the most relevant rights affirmed by the GDPR, finally, is that the individual will not be subject to a decision based solely on automated processing, including profiling which leaves decision making to humans. These principles may challenge the application of AI interventions, which work on a complex intersection of data that may be difficult to justify[57].

8. Shaping the informed consent for AI interventions

The aforementioned observations pose unique challenges in the development of informed consent for AI based interventions. In order to make decisions regarding medical procedures to undergo, patients should be properly informed about risk and benefits and should be acknowledged about different options. The obvious benefit of AI intervention is the potential to be superior to routine clinical practice. The downside include potential cyberattacks, which became more frequent during the Covid-19 pandemic, and error, due to bias in the development and training of algorithms, which is also exacerbated by the Covid-19 pandemic. However, an appropriate communication on the risk/benefit analysis should be based on probabilities that a specific event occurs which, unfortunately, is very difficult to estimate for these risks.

Another challenge in developing an informed consent for AI interventions is explaining how certain tools work. The "black box" problem makes the explanation of the mechanism difficult. Moreover, the majority of medical doctors are not knowledgeable on the basic principles of AI[58]. This observation calls for the need by clinicians to disclose to which extent they can interpret the recommendations provided by AI systems[59].

If explainability may be an issue in adult patients, it becomes even more difficult when patients are in pediatric age and assent should be obtained from them. Many of the existing AI therapeutic interventions (digital therapeutics) are developed for diseases in childhood and will increasingly need to be tested in clinical trials. An effort should be made in improving explainability of AI interventions tailoring the informed consent to different age groups and profiles.

[56] J. Sunrise Winter, E. Davidson, *Governance of Artificial Intelligence and Personal Health Information, Digital Policy, Regulation and Governance* 21, no. 3 (1 January 2019): 280–90.

[57] M. Bourassa Forcier et al., *Integrating Artificial Intelligence into Health Care through Data Access: Can the GDPR Act as a Beacon for Policymakers?,* in *Journal of Law and the Biosciences* vol. 6, no. 1 (2019), 317-335.

[58] D. Schiff and J. Borenstein, *How Should Clinicians Communicate With Patients About the Roles of Artificially Intelligent Team Members?,* in *AMA Journal of Ethics 21,* no. 2 (1 February 2019): E138-145.

[59] S. Gerke, T. Minssen, and G. Cohen, *Ethical and Legal Challenges of Artificial Intelligence-Driven Healthcare,* in *Artificial Intelligence in Healthcare,* 2020, 295–336.

While the focus of informed consent is providing the best information to patients in order to make their own decisions, the possibility that a patient withdraws from a study including training algorithms, creates a potential problem. Indeed, patients no longer participating in clinical trials have the right to have all their data deleted. This may create a problem in updating algorithms when they have been already trained and deployed.

It is likely that the use of electronic tools based on AI will be increasingly accompanied by electronic consent processes. On one hand, these tools have the potential to improve the understanding of patients using multimedia and verification tools[60]. On the other hand electronic consent without the supervision of a health professional in person, should be carefully developed to include all details relevant of AI interventions which may be challenging[61].

Blockchain may be an interesting solution for data transactions, not necessarily specific for AI interventions, which secures privacy of users, immutability of transactions, and personalization of data access through smart contracts. As AI systems may result from a combination of data from different sources and there is the potential for reuse of data, blockchain may represent a safety net in clinical studies. Moreover, blockchain is increasingly considered as a technology supporting the informed consent process that allows tracking of the process itself and that may help to provide consent at multiple levels and for different purposes[62].

9. Conclusions

The explosion of AI technologies for healthcare will require an increasing number of clinical trials to compare AI based tools with existing best practices. At present, the existing recommendations and tools for the informed consent process are not perfectly tailored for these studies. A crucial role in satisfying the needs of these studies should be played by Institutional Review Boards and from Ethical Committees. It will be essential that these boards and committees will include participants with both a technical knowledge of AI systems, and a specific ethical background in this area. Such a result not only requires a multidisciplinary approach, but also a new impulse to acquire a proper knowledge in AI by diverse professionals involved in ethical decisions of AI studies. This approach should improve the content and the understanding of informed consent forms for these studies. A second need will be providing precise and thorough information to participants in clinical trials through personal communication, which is usually made by a clinician. The complexity of AI mechanisms and their difficulty to be explained may add to the scarce familiarity of clinicians with AI topics. It is clear that education activities focused on the use of AI in healthcare and on ethical implications are strongly needed for addressing these challenges since they carry completely different characteristics compared with traditional diagnostic and therapeutic interventions.

Due to the need to limit personal contacts, the Covid-19 pandemic has created pressure on the deployment of digital tools for clinical trials that can be managed remotely. This pressure has raised

[60] F. Gesualdo et al., *Digital Tools in the Informed Consent Process: A Systematic Review',* in *BMC Medical Ethics* vol. 22, no. 1 (27 February 2021): 18.

[61] S. Gerke, T. Minssen, and G. Cohen, *Ethical and Legal Challenges of Artificial Intelligence-Driven Healthcare.*

[62] P. V. Kakarlapudi and Q. H. Mahmoud, *A Systematic Review of Blockchain for Consent Management,* in *Healthcare* (Basel, Switzerland) 9, no. 2 (1 February 2021).

the interest in virtual and hybrid clinical trials and will possibly accelerate the transition from in person activities to digital trials helping to streamline costs, efforts and time, conducting to a wider patients' engagement and faster results. One interesting implication of remoting clinical trials is the opportunity to collect a wide array of data reported by patients or from sensors, creating rich databases that will require a specific effort for the analysis. On the other hand, the lack of personal encounters in virtual clinical trials may create communication problems between the patients and the investigators.

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Special issue

The bioethical and bio-juridical debate regarding the use of biological samples and data for the purpose of genetic research on human health: open problems

Monica Toraldo di Francia*

ABSTRACT: Among the categories of personal data, a special status is recognized to genetic information, as genetic identity is a relational identity; personal genetic information is structurally shared with other subjects belonging to the same "biological group" and moreover in this kind of information knowledge and prediction of the risk of getting sick are intertwined. For this reason, biological samples, and the genetic personal data connected to them, are subject to special protection which makes the question of regulating their acquisition, storage, use, distribution and sharing specifically complex. Focusing on this issue of great general bioethical importance, particularly in the current context of the Covid-19 pandemic, the article highlights some theoretical-philosophical problems which underlie, from the very beginning, the bioethical and bio-juridical debate regarding both the status of biological samples donated for genetic research purposes, and the right of sample donors to choose whether or not to know individual results of potential clinical relevance; these issues are explored with special reference to genetic research with minors.

KEYWORDS: Biological samples, genetic information, genetic research with minors, the right not to know

SUMMARY: 1. Introduction – 2. The ethical and legal "status" of biological samples and genetic information – 3. A controversial right: the "Right Not to Know" – 4. Genetic research with minors and the right not to know – 5. Still on "minors": the gap between abstract principles and praxis.

1. Introduction

As a philosopher and bioethicist, I will try to highlight in this article some theoretical-philosophical problems which underlie, from the very beginning, the bioethical and bio-juridical debate regarding both the status of biological samples donated for genetic research purposes, and the right of sample donors to choose whether or not to know individual results of potential clinical relevance. This is an issue of great general bioethical importance,

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particularly in the current context of the Covid-19 pandemic. In the context of the Covid-19 pandemic, numerous biological samples are taken, also in the context of diagnoses and epidemiological investigations, by means of swabs and /or blood samples, as well as in the context of trials for therapeutic purposes. The Italian National Committee for Bioethics has recently produced specific recommendations regarding the use of biological samples in the context of the Covid-19 pandemic[1].
To illustrate the bioethical and bio-juridical framework of the problem, I propose to emphasize only a few significant moments of this ongoing comparison of positions to highlight the reasons for the uncertainties and ambiguities of legislation on a subject that is always *in fieri*[2]. My idea is that even the most recent directives[3] are not exempt due to the difficulty in reconciling the various competing rights and interests in a balanced and generalized way: those of the subjects who donate their samples not to lose control over their use and related personal information / those of the researchers not to have too many constraints / those of patients without effective therapies to accelerate the research and discovery of new life-saving therapies / those of the pharmaceutical industry to realize patents and profits.
In the last part I will consider instead the difficulties encountered by ethics committees when they review the genetic studies of projects that involve the participation of a category of particularly vulnerable subjects: that of the so-called "minors" (newborns, children, adolescents).

2. The ethical and legal "status" of biological samples and genetic information

The ambiguities that still remain regarding the legal status of biological samples used for scientific research and clinical studies have their roots in the centuries-old debate on the status of the human body, always oscillating between dichotomous visions that throughout history have been, depending on the contexts, the subject of multiple philosophical, anthropological, religious, economic, legal arguments in favor of one or the other concept: the body as "me", as subject, as intrinsic value/as

[1] See ITALIAN COMMITTEE FOR BIOETHICS, *Biomedical research for novel therapeutic treatments within the Covid-19 pandemic: ethical issues*, Opinion 22 October 2020, available at http://bioetica.governo.it/en/opinions/opinions-responses/biomedical-research-for-novel-therapeutic-treatments-within-the-covid-19-pandemic-ethical-issues/ (last accessed on June 1st, 2021).

[2] For an analysis and an updated discussion of the legal issues regarding the use of genetic information, see M. TOMASI, S. PENASA, A. O. COZZI, D. MASCALZONI (eds.), *Law, Genetics and Genomics: An Unfolding Relationship,* in *BioLaw Journal-Rivista di BioDiritto,* Special Issue no. 1, 2021, pp. 460, available at http://rivista.biodiritto.org/ojs/index.php?journal=biolaw (last accessed on June 1st, 2021).

[3] *European Union Regulation no. 536/2014 on clinical trials of medicinal products for human use, which repeals Directive 2001/20/EC*; *Regulation* 679/2016 *of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data, as well as the free circulation of such data, which repeals Directive 95/46/EC (General Regulation on Data Protection*); THE COUNCIL OF EUROPE-COMMITTEE OF MINISTERS, *Recommendation to member States on research on biological materials of human origin* CM / Rec (2016) 6; COUNCIL OF INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCE (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans*, Council of International Organizations of Medical Science (CIOMS), Geneva, 2016, available at https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. These are European and international documents which are binding to very different degrees, but to which I will refer to from time to time in this article regardless of this distinction.

"not-me", as an object of property, as a commodity[4]. These different visions further complicate, giving rise to additional questions, when, in the era of bio-techno-sciences, it becomes possible to break down the body into parts, tissues, cells, products that can live their own extra-corporeal life in time and space, undergo transformations and be used in multiple ways for one's own benefit and/or that of others[5].

Not being able to enter into the merits of a discussion that is continually re-proposed from various disciplinary angles, I will limit myself to considering, in this light, the question of the moral and legal status of biological samples 'donated' for the purpose of research, focusing attention on genomic and postgenomic research and clinical trials. Here a peculiar category comes into play, that of "belonging", which evokes a link of pertinence of the sample to the I of the donor: the "donated" biological sample is something that is both me and not me, because, even if separated from me, it is also always a place of identity, a place of genetic identity, and as such is worthy of particular protection[6]. From a legal point of view, this concept supports the interpretation according to which the subject "donates" his/her own sample in the form of a concession of use under established conditions, that is, to the extent to which consent is given; a formula, which contemplates the right to control the use of the sample, access personal data and their possible correction, together with provision of the possibility to withdraw, at any time, the consent initially given and request the return or destruction of the donated sample. Informed consent must therefore cover the entire path of the sample, including the phases of collection, storage, use and possible transfer to other researchers or institutions and, also,

[4] G. Berlinguer, V. Garaffa, *La merce finale. Saggio sulla compravendita di parti del corpo umano*, Milan, 1996. See also, just to give some examples of a large and articulated debate still underway, L. Andrews and D. Nelkin, *Body Bazaar. The Market of Human Tissue in the Biotechnology Age,* New York, 2001, Italian translation *Il mercato del corpo,* Milan, 2002; M.C. Mazzoni (ed.) *Per uno statuto del corpo*, Milan 2008. Also of interest is the discussion on the licitness or otherwise of the commercialization of parts, functions and products of the human body, which took place in the joint meeting of the Forum of National Ethics Councils (NEC Forum) with the European Group on Ethics in Science and New Technologies (EGE), held in Brussels in October 2010.

[5] In fact, we are immediately faced with an intricate knot of problems which, if on the one hand refer to the more comprehensive concept of the 'person' and personal identity, on the other they are intertwined with very concrete practical interests, of the market and research, regarding the patentability of 'inventions' that incorporate, or reproduce genetic sequences, or human biological materials. The legal status of the human body seems to emerge, however, from this matter, pervaded by ambiguity, even limiting attention exclusively to the scope of European legislation and the comparison between the Oviedo *Convention* and the later Directive of the European Parliament and the Council (98/44/EC) on the legal protection of biotechnological inventions. See, in this regard, M. Tallacchini, *Habeas Corpus? Il corpo umano fra non-commerciabilità e brevettabilità*, in *Bioetica. Rivista interdisciplinare*, vol. 6, no. 4 (1998), pp.531-552. Always in this regard, M. Toraldo di Francia, *Valori costituzionali e "diritto" all'identità personale*, in F. Cerutti (ed.), *Identità e politica*, Roma-Bari, 1996 pp. 113-129, identifying in the continental European constitutional model of the second post-war period, and in the conception of the person as a synthesis of underlying individuality and relationality, the guiding criteria for addressing some of the most controversial issues raised by the innovation of bio-techno-sciences and the evolution of the ethical-cultural perspectives informing today's liberal democratic societies. Along the same lines M. Tomasi, *Genetica e costituzione: esercizi di eguaglianza, solidarietà e responsabilità*, Naples, 2019.

[6] P. Zatti, *Il corpo e la nebulosa dell'appartenenza: dalla sovranità alla proprietà*, in C.M. Mazzoni (ed.), *Per uno statuto del corpo, cit.,* pp. 69-108; S. Rodotà, *Persona e identità genetica*, in G. Bonacchi (ed.), *Dialoghi di bioetica*, Rome, 2003, pp. 19-23.

make clear the possibility or exclusion of a return of information of individual interest to the donor on the results of the research/trial[7].

Without prejudice to the fact that the donation is always to be understood as a free, informed, gratuitous act of social value[8], the question remains open regarding whether or not it is licit, from a strictly bioethical standpoint, to include in the informed consent for genetic studies also the option of an explicit and irreversible donation of one's samples; or rather a broad consent for any future studies not yet foreseeable, which precludes further contacts with the donor and which, in fact, in many cases involves the waiver of any claim of control over the use and fate of one's biological material and related information[9].

The question of the singularity or otherwise of the genetic information drawn from the samples under study with respect to other types of information concerning health cannot be separated from this issue; such singularity would legitimize special protection within the category of the so-called "sensitive" personal data. Despite some discordant voices[10] in most national, European and supranational documents there is agreement on recognizing to this category of data a particularly strong legal status, by virtue of the particular nature of this type of information which, although, it defines the individual in his/her genetic uniqueness, at the same time it puts the individual in relation with other subjects belonging to the same pattern of inheritance[11].

There are two salient aspects of this peculiarity:

i. the presence of a close intertwining between knowledge and prediction, since genetic information allows us to know in advance certain aspects concerning one's biological future, whether in terms of increased susceptibility, compared to the average, to developing certain diseases (or even a resistance to the same diseases), or being predestined to becoming ill and an early death, in the case of monogenic diseases with a variable onset which to date are neither preventable nor treatable;

[7] Italian Committee for Bioethics (ICB) and the National Committee for Biosafety, Biotechnology and Life Sciences, (ICB-CNBBSV Joint Group), *Collection of biological samples for research purposes: informed consent, Joint Opinions ICB/ICBBSL*, 16 February 2009; The Council of Europe, *Recommendation to member States on research on biological materials of human origin, cit.*; Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Health-related Research Involving Humans*, *cit.*

[8] Council of Europe- Committee of Ministers, *Recommendation 2016/6*, cit. For a detailed reconstruction of the regulatory framework of reference for research and experimentation involving human beings, both before and during the pandemic emergency, see L. Palazzani, *Informed consent in biomedical research in the pandemic context. Between bioethics and biolaw*, in *BioLaw Journal – Rivista di BioDiritto*, Special Issue 2/2021, p 3-15.

[9] Both the already quoted *Recommendations on research on biological materials of human origin* and the *International Ethical Guidelines for Health-related Research Involving Humans* recognize as legitimate, albeit with some restrictions, the option of *broad consent* to the storage and use of samples for future research not yet foreseeable. But the reference, in these two documents, seems to relate exclusively to biobanking in known and certified locations and not to sending the samples directly to the large pharmaceutical companies that sponsor the research.

[10] For example, E. McNally, A. Cambon-Thomsen et al., *Recommendations on the Ethical, Legal and Social Implications of Genetic Testing*, *Official publications of the European Communities*, Luxembourg, 2004; Working Group for the American College of Medical Genetics and Genomics, *Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*, in *Genetics in Medicine*, 2013, 15, n. 7, pp. 565-574.

[11] S. Rodotà, *Lo statuto delle informazioni genetiche*, in G. Bonacchi (ed.), *Dialoghi, cit.,* pp. 241-47 and Id., *La vita e le regole. Tra diritto e non diritto*, Milan, 2006.

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ii. the fact that genetic identity is a relational identity, as personal genetic information is structurally shared, to some extent, with other subjects belonging to the same "biological group", which is why knowledge of one's own genome may also require the acquisition of information regarding other relatives and/or sharing with them the results of individual genetic analyzes of clinical utility[12].

This peculiarity makes the question of regulating access to such information and its circulation and use even more delicate, especially if one takes into account that the "donated" samples in order to be of use to genomic and post-genomic research, must always be accompanied by a series of data, on the person (age, sex, ethnicity ...), health, lifestyles and living environment, related to the donor. Even in the presence of strict regulations for the protection of sensitive and "highly sensitive" personal information and of standardized procedures for the coding of samples (pseudo-anonymisation, or other solutions), so that direct access to the donor's identity is only reserved to those who are authorized, if there is an explicit and irreversible donation of one's samples, it is difficult to guarantee an adequate level of protection of the data subject's privacy, such as to exclude improper use of samples and data, with possible discriminatory consequences for the donor (for example, in terms of employment or access to goods and services such as health or life insurance)[13].

3. A controversial right: the "Right Not to Know"

Another area in which the discussion on the management of biological samples and related data is open to comparison between different positions is the debate on the legitimacy and possible limitation

[12] On the possible conflicts between the competing interests of persons belonging to the same "biological group", M. TORALDO DI FRANCIA, *La sfida delle biotecnologie: identità, conflitti e nuove forme di discriminazione*, in D. BELLITTI (ed.), *Epimeteo e il Golem. Riflessioni su uomo natura e tecnica in età globale*, Pisa, pp. 276-283.

[13] The issue of the prohibition of genetic discrimination is also at the center of the many regulations and guidelines that have followed one another over time; as regards biomedical research, in addition to *the Convention on Human Rights and Biomedicine* (art. 6 *Non discrimination*), see THE COUNCIL OF EUROPE, *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research,* art. 5, which underlines how the risks of discrimination or stigmatisation cannot be excluded even if the data are anonymised; in the Explanatory Report of art. 4 *Non-discrimination and non-stigmatisation*, of the THE COUNCIL OF EUROPE, *Additional Protocol concerning Genetic Testing for Health Purposes* (2008), the difference between the two concepts is then well clarified: "*The concept of discrimination relates to a difference in the treatment of the person concerned. Yet not all differences in treatment necessarily amount to discrimination [...]The concept of 'stigmatisation' rather relates to the way in which a person or group is perceived on the basis, in this case, of their genetic characteristics, whether these exist or are thought to exist. It takes, in particular, the form of words or acts that negatively label a person or group of persons on account of their known or supposed characteristics*". More recently, again on the prohibition of discrimination or stigmatisation on the basis of genetic characteristics, see article 5 of the *Recommendation on research on biological materials of human origin and Guideline 24 of the International Ethical Guidelines for Health-related Research Involving Humans*. On the problem of the possible discriminatory consequences towards persons and groups, if the applicant request by private insurance companies to be able to use the results of genetic analyzes for the assessment of insurance risk were accepted, cfr. the detailed and still current opinion of the Joint Opinion ICB/ICBBSL, *Genetic tests and insurance*, 20 October 2008, which highlights how, behind the problem outlined, there are broader concepts of the relationship between market and 'privacy', between market and protection the rights of the person in a state of vulnerability.

of the "right not to know", in our case, the right of those participating in research/trials to choose not to know at all, or in part, the results of the genetic analysis of their biological samples, including information derived from the so-called Incidental Findings (IF); that is, from those "incidental" results, of potential clinical relevance, which emerge outside the scope of the original purposes for which the research or trial was conducted and which due to the development of second generation sequencing techniques has become increasingly frequent[14].

As is known, this is a relatively recent right, which follows the recognition of the right to be informed and the achievement of informed consent as a principle of legitimacy for medical intervention[15]. Only in 1997 did the Right Not to Know, characterized as an aspect of personal autonomy, gain its first recognition – to be followed by many others - in the *Universal Declaration on the Human Genome and Human Rights* of Unesco (Article 5) and, in the same year, in the *Convention on Human Rights and Biomedicine* (Article 10) of the Council of Europe. Nevertheless, in the bioethical and bio-juridical debate, the plausibility of the Right Not to Know continues to be a controversial matter due to the continuing lack of agreement on the ethical-philosophical meaning of the concept of "autonomy" and on the rights and/or interests to be protected that derive from it[16].

The most articulated discussion on the subject was developed during the *Symposium From the Right to Know to the Right Not to Know*[17], held in Canada in spring 2014 as a response to the *Recommendations for reporting of incidental findings in clinical exome and genome sequencing*, released one year earlier by the Working Group of the American College of Medical Genetics and Genomics[18], which denied the possibility of exercising the Right Not to Know in the case of genomic sequencing.

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[14] The possibility of incidental results has arisen above all in conjunction with the very rapid evolution of second generation genomic sequencing technologies, which, in recent years, have transformed and accelerated the research and diagnosis of many diseases. While in the past it was possible to analyze only single segments of DNA, new techniques now make it possible to decrypt the entire exome (*Whole Exome Sequencing*, WES), or even the entire genome (*Whole Genome Sequencing*, WGS), including the coding and non-coding sequences of a person (ICB, *Management of "incidental findings" in genomic investigations with new technology platforms*, 17.03.2016). On the problems raised by new sequencing techniques and the management of 'incidental findings', C.G. VAN EL ET AL., *Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics*, on behalf of the ESHG Public and Professional Policy Committee, in *European Journal of Human Genetics* vol. 21 (2013), pp. 580–584.

[15] For an in-depth analysis of the right not to know in a constitutional perspective and in relation to the implications for informed consent, cfr. the recent essay by A. O. Cozzi, *Incidental Findings and the Right Not to Know in Clinical Setting: Constitutional Perspectives*, in *BioLaw Journal-Rivista di BioDiritto*, Special Issue no. 1/2021, pp. 79-109, available at http://rivista.biodiritto.org/ojs/index.php?journal=biolaw&page=article&op=view&path%5B%5D=776&path%5B%5D=646 (last accessed on June 1st, 2021).

[16] Italian Committee for Bioethics, *Managing Incidental Findings*, Managing "Incidental Findings" in genomic investigations with new technology platforms, Opinion, March 17th 2016.

[17] B.M. KNOPPERS, *Introduction from the Right to Know to the Right Not to Know,* in *The Journal of Law, Medicine & Ethics*, Vol. 42, no 1, Spring 2014, pp. 6-10.

[18] WORKING GROUP OF THE AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS, *Recommendations*, cit., then partially revised by the same Board of Directors of AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS, *Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results*, Bethesda, 2014, April 1, https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf (last accessed on June 14th, 2021).

The Symposium, which took place with the participation of scientists, jurists and moral philosophers, marked an important stage in the process of conceptual clarification of the misinterpretations and misunderstandings that had hitherto vitiated the debate on this controversial right and its theoretical presuppositions. In this regard, it emerged that it is precisely these divergent ethical-philosophical interpretations of the concept of "autonomy" which found on conflicting ethical principles both the arguments for and against the recognition of the Right Not to Know. In summary, there are three main interpretations of the concept, which in turn envisage different ideals of what is meant by the expression "autonomous decision" and different, or conflicting, conclusions regarding the regulatory relevance of the Right Not to Know.

For the first ideal, what is of value, and worthy of protection, is non-interference in the most intimate and personal decisions; in this case, autonomy coincides with the personal freedom of the adult and competent individual to decide his/her own life and, therefore, requires a regulatory policy which guarantees these corresponding rights, including the right to refuse to receive information concerning one's own health.

Much more demanding is the interpretation that connects the concept of autonomy to an ideal that requires competent persons, as moral agents, to control the circumstances of their own existence. For this conception, people not only have the right, but also the duty to know as much information as possible about their state of health, including genetic conditions, in order to be able to exercise "self-governance" and make rationally founded decisions, that is, based on all potentially relevant obtainable information for the prudent planning of one's existence. This excludes a priori the possibility of morally establishing the claim of being able to remain in ignorance[19].

But there is also a third conception, often unrecognized, opposite to the one previously illustrated, which links autonomy to an ideal of "authenticity". This interpretation finds, in the philosophical context, its most accredited supporter in Hans Jonas. Already in the 1970s, faced with the accelerated progress of biomedical technologies that seemed to be able to question the "right of each human life to find its own way and be a surprise to itself"[20], Jonas had envisaged the emergence of a new moral right, that of ignorance of one's future; a right which, in certain situations - for example when the information on late-onset genetic diseases currently not preventable or curable is at stake - can present itself as a precondition for the free construction and definition of the self[21].

[19] J. Harris, K. Keywood, *Ignorance, Information and Autonomy,* in *Theoretical Medicine and Bioethics*, vol. 22, no. 5, 2001, pp. 415-436. Position maintained by the authors also thereafter.

[20] H. Jonas, *Philosophical Essays*. *From Ancient Creed to Technological Man*, Chicago, 1974, Italian translation *Dalla fede antica all'uomo tecnologico*, Bologna, 1991, p. 251.

[21] The aspect of the 'right not to know' that relates to delicate psychological profiles, of ethical and legal importance, was dealt with in ICB-ICBBSL, *Genetic testing and insurance*, cit. Inescapable is the question of how the knowledge of one's genetic predisposition to certain diseases and this same perception, and being perceived by those closest, as subjects predestined to an inauspicious fate, can reflect on and condition the development of one's sense of self, one's self-esteem and identity, coercing life and relationship choices in advance. On the interest in not knowing genetic information about oneself, due to the possible negative psychological and social consequences deriving from this knowledge, cfr. N. Juth, *The Right Not to Know and the Duty to Tell: The Case of Relatives,* in *Journal of Law, Medicine & Ethics,* vol. 42, no. 1, pp. 38-52; this article also addresses the issue of the difficult balance between the many interests at stake, individual, family, group, in relation to the question of knowing/not knowing the results of genetic analyzes of possible interest for health or for reproductive choices.

If the second interpretation is incompatible with the recognition of the right not to know, for the other two this right finds instead a foundation - at least as a "prima facie" right, subject to exceptions in particular circumstances[22] - in the negative freedom of the subject in the one case, and in the "existential" freedom of self-determination based on one's values in the other.

However, if we move from the abstract to the factual level of the concrete dilemmas that can arise when researchers and clinicians find themselves having to decide whether or not to communicate the "incidental" results arising from a genetic investigation, the aforementioned concepts do not help to resolve the question of the decision to be taken in the absence of an explicit expression of will on the part of the person concerned to be or not to be informed about this[23]. In these situations, the justification of the Right Not to Know cannot be based solely on the principle of autonomy, as there is no choice; hence the proposal to found the justification of the Right Not to Know also on a different theoretical basis, or rather on the interest in respecting privacy, understood as the separation of the "private" sphere including the individual psychological dimension, not accessible to others except for good reasons, which must always be argued[24].

It is therefore suggested that, faced with the dilemma of whether or not to communicate the unsolicited results of genetic analyzes, the professional in possession of this information (researcher, geneticist ...) should carefully evaluate, case by case and with the help of other consultants, the reasons for communicating /not communicating them to the person most directly concerned, in the awareness that any decision in this regard could also be of interest to others belonging to the same family circle. In this decision, the type of information in question must therefore play a significant role, depending on whether it is data of clinical utility for early prevention, or because there is the possibility of a therapy, or instead, it concerns predictive data for late-onset diseases for which there is currently no treatment but which could prove indispensable in order to make informed reproductive choices, or

On the difficulties encountered, more generally, in the protection of the 'right not to know', in the reshaping of our mutual responsibilities, cfr.r. M. TORALDO DI FRANCIA, *Sviluppo delle bio-tecno-scienze genetiche e cittadinanza,* in *Homo medicus e commodification. Una prospettiva bioetica*, in *Jura gentium*, vol. 17, no. 1 (2020), pp. 187-94. The danger of a loss of relevance of the right to not know was also highlighted by the UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights*, 2 October 2015, available at https://unesdoc.unesco.org/ark:/48223/pf0000233258 (last accessed on June 14th, 2021), which underlines how the possibility of knowing one's genomic constitution can raise the social expectation that people plan and live their lives in accordance with this knowledge. Such an expectation could not only make one lose sight of the importance for health of the multiple social determinants that affect it, but also lead to discrimination and stigmatization of those who do not adopt a "*health-promoting lifestyle*".

[22] E.g. when it comes to information on serious diseases that can be avoided with early prevention, or for which there are effective treatments.

[23] Cfr. M. TORALDO DI FRANCIA, *Genetica Caso 4: Test genetici per malattie a insorgenza tardiva*. *Il punto di vista bioetico; Consenso all'atto medico*, in P. FUNGHI, F. GIUNTA (ed), *Medicina, bioetica e diritto. I problemi e la loro dimensione normativa*, Pisa, 2012, pp 84-90, where this possibility is taken into consideration and possible responses to the dilemma of communication / non-communication to the person directly concerned are examined.

[24] Cfr. J. LAURIE, *Recognizing the Right Not to Know: Conceptual, Professional, and Legal Implications*, in *The Journal of Law, Medicine & Ethics*, cit., pp. 53-63; G. HELGESSON, *Autonomy, the Right Not to Know, and the Right to Know Personal Research Results: What Rights Are There, and Who Should Decide about Exceptions?,* in *The Journal of Law, Medicine & Ethics*, cit., pp. 28-37.

even predictive data of a disease risk that cannot be quantified at an individual level, or with clinical implications that are still uncertain (the so-called VUS, *Variant of Uncertain Significance*).
Ultimately, however it is justified, the right or interest of adults and "capable" individuals not to know is always considered by its supporters as a *prima facie* right or interest, to be respected in most cases, but which can always encounter limitations in particular situations.

4. Genetic research with minors and the right not to know

The question of respecting the Right Not to Know becomes even more complicated when it comes to research involving the sequencing of the biological samples of a category of subjects to whom special protection is due, that of minors. It being understood that when we talk about research involving minors we must always keep in mind the heterogeneity of this category, which extends from newborns to adolescents on the threshold of adulthood, including subjects with very different physical, cognitive and emotional abilities, there are certain ethical principles that are valid in general for the whole category, first of all the ethical principle of respecting the "best interests" of the minor participating in a research/clinical trial[25]. If this is the guiding principle to be followed also in genomic studies, there is good reason to believe that these interests include not only ensuring minors the possibility of deciding on coming of age whether or not to consent to further conservation-use of their biological samples and data, but also the interest not to know, also defined as the "right to an open future"[26], when the information resulting from the analysis of the samples is not immediately useful for their health[27]. The possible negative effects of such information, for example in the case of the prediction of non-preventable late-onset diseases, include damage to self-esteem, the ability to form meaningful future relationships, the relationship with parents, as well as the loss of privacy and future autonomy. However, the minor's interest "not to know" may, in some cases, conflict with the parents' interest to know the same information to plan their reproductive choices and there is no agreement of views on which of the two interests should prevail in this particular circumstance[28]. What emerges from the bioethical and biojuridical debate on this is, in fact, a clear contrast between two conceptions of the concept of "clinical utility" as a criterion for communicating/not communicating the results of a genetic analysis. On the one hand there are those who still consider valid the classic criteria according to which the clinical utility of an investigation refers to the identification of conditions for which there is immediate availability of treatment, or effective preventive measures; and on the other hand, those who intend to extend its meaning to include information on conditions that do not require immediate medical intervention, or that lack effective treatments, or are not clearly pathological and whose recipients, in terms of the possible benefits to be taken into consideration, involve not only the parties

[25] THE COUNCIL OF EUROPE-COMMITTEE OF MINISTERS,*Recommendation* CM/Rec(2016)6, cit.
[26] J. FEINBERG, *The Child's Right to an Open Future*, in W. AIKEN, H. LAFOLETTE (eds.), *Whose Child? Children's Rights, Parental Authority, and State Power*, Totowa, 1980, pp. 124-153.
[27] See in particular P. BORRY, M. SHABANI, AND H. C. HOWARD, *Is There a Right Time to Know? The Right Not to Know and Genetic Testing in Children,* in *The Journal of Law, Medicine & Ethics,* cit., pp. 19-27.
[28] On the difficulty of balancing the autonomy and interests of the child with the needs and rights of parents C.G. VAN EL ET AL., *Whole-genome sequencing in health care Recommendations of the European Society of Human Genetics,* cit.

directly concerned, but also their family members. In this second perspective, which now seems to prevail, "all the so-called 'actionable' information, i.e., such as to prefigure a decision-making intervention by the person concerned and/or his family members (reproductive decisions, planning of life choices, insurance plans, etc.), are included in the category of information of clinical usefulness and, therefore, to be communicated"[29].

In my opinion, the ethical issue remains open as regards whether or not it is licit to extend the meaning to encompass the parents' need for knowledge for reproductive purposes, needs which, in the case of conflict, can prevail over the protection of the minor's "best interest".

5. Still on "minors": the gap between abstract principles and praxis

Still with regard to the category of "minors", further difficulties can be pointed out relating to the gap between the rights whose protection every research project should guarantee, according to the legislation in force[30], and what in actual fact becomes increasingly difficult to ensure to the participants who donate their samples.

Given that research with minors must comply with all the conditions already provided for "capable" adults (such as, for example, the absence of undue pressure inducing participation, the possibility of withdrawing consent already given at any time, the right to know information of individual interest to health that may derive from research, especially in the case of genetic research[31]), there are additional conditions, supplementary to the informed consent of the parents or legal representative, for this type of study to be considered morally acceptable by the Ethics Committee appointed to undertake the review:

1. research cannot be carried out with comparable efficacy on subjects capable of giving legally valid informed consent;

2. the expected results of the research deliver a real and direct benefit for the minor, or otherwise, the research must have the aim of contributing, through significant improvement in the scientific knowledge of the person's condition, illness, disorder, to obtain results that may be of benefit to other people of the same age group, or who suffer from the same disease or disorder, or have the same

[29] The Italian Committee for Bioethics, *Managing Incidental Findings*, cit.

[30] World Medical Association, *Declaration of Helsinki. Ethical principles for medical research involving human subjects*, 1964 (last revision 2013), available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last accessed on June 1st, 2021).

[31] On the latter point, see The Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research,* cit., Art. 27 "*Duty of care*". The CIOMS Guidelines note that, in the case of genetic research, there is a growing consensus in favor of the duty of researchers to at least provide for the communication of certain types of information deriving from the study, if this is the desire of the donor of the sample. In general, the three main guiding criteria in this regard require that the results have analytical validity, clinical significance and are 'actionable'; it will then be up to the competent Ethics Committee to assess whether or not there is the need to provide genetic counselling contextual to the communication (Guideline 11).

characteristics and the research must entail only minimum risk and minimum burden for the minor involved[32];

3. the opinion of the minor must be taken into consideration as a factor of increasing importance in relation to his/her age and degree of maturity[33];

4. the minor does not object[34].

As for the return of possibly useful information for the health of the minor – there is always reference to genetic research - frequently in the protocols resort is made to the clause regarding the non-clinical purpose of the study in order to deny this right to the person concerned, whereas it would be only right to communicate these data, if requested, especially when the investigation concerns small groups of patients as in the case of investigations on rare diseases.

The ethics committees for paediatric clinical trials also encounter other difficulties when it comes to ascertaining, in the case of studies where there is no real and direct benefit for the donor, that the research involves only a minimal risk for the person concerned, even in terms of his/her right to the protection of privacy; or, again, when they find it necessary to exclude the exercise of direct or indirect pressure on parents, especially when the researcher is also the patient's doctor, or there is a need to recruit "healthy" control subjects for comparison, as often happens in genetic clinical studies with the collection, storage and use of biological samples and related data[35].

As regards, on the other hand, the real possibility of guaranteeing the right to revoke consent already given for present and future research, which provides for the right to request the return or destruction of the donated biological sample and non-use for further studies of the personal information collected,

[32] Still Guidelines 17, of the CIOMS Guidelines, permits, however, the possibility that the competent Ethics Committee approves a 'minor increase' above 'minimum risk', if the scientific and social value of the research is of the utmost importance and it is not possible to achieve the goal in another way.

[33] On the basis of these provisions, the pediatric ethics committees may request the preparation of disclosure-assent forms that are differentiated for the different age groups (7-13; 14-17), in addition to those intended for parents /legal guardian. In the Commentary on Guideline 17 of the *International Ethical Guidelines* it is pointed out that: *"the process of obtaining assent must take into account not only the age of children, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation. As adolescents near the age of majority, their agreement to participate in research may be ethically (though not legally) equivalent to consent. In this situation, parental consent is ethically best considered as "co-consent" but legally, the adolescent's agreement remains assent".*

[34] As stated in the Explanatory Report of the *'Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research*, in the case of newborns and very young children the parents will have to decide taking into account, of course, other factors, while the commentary on Guideline 17 adds that: "*a deliberate objection by a child or adolescent to taking part in research must be respected even if the parents have given permission, unless the child or adolescent needs treatment that is not available outside the context of research, the research intervention has a clear prospect of clinical benefit, and the treating physician and the legally authorized representative consider the research intervention to be the best available medical option for the given child or adolescent. In such cases, particularly if the child is very young or immature, a parent or guardian may override the child`s objections. However, in some situations parents may press a researcher to persist with an investigational intervention against the child`s wishes. Sometimes this pressure is meant to serve the parents' interests rather than the child's. In this case, the parents' decision must be overridden if the researcher believes it is not in the child's best clinical interest to enrol or continue study participation".*

[35] Cfr. M. TORALDO DI FRANCIA, *Note sulla mia esperienza in un Comitato etico per la sperimentazione clinica pediatrica*, in *Forum: Le responsabilità nei confronti della scienza*, in *BioLaw Jounal/Rivista di BioDiritto*, 1/2017, pp. 29-33.

including codified information, it should be noted that in disclosure and informed consents, often clauses are set preventing its enforceability'[36]. While recognizing this right to the parent/legal representative, Sponsors[37] can protect themselves - and this is what often happens when the Sponsor is a large pharmaceutical company with biobanks and analysis laboratories located in several countries – by already warning in the disclosure that it could be unable to guarantee their return-destruction, not only because the samples may have been anonymised, but also because they may no longer be under the Sponsor's responsibility because they have already been released to a third party. In this way, not only is the traceability of the samples lost, with the joint risks of improper use as mentioned above, but the minor is also deprived of the opportunity, on reaching the age of majority, to give new consent to their conservation, transmission, use.

To end on a more personal note, I hope that once we are out of this pandemic thought can be given to what the health emergency has taught us, distinguishing between what is justified to request in times of a pandemic, in the name of a more general common good, and what in "normal" times might no longer be appropriate to recommend, particularly when biomedical research involves minors; I am referring, in this regard, to the request to share with the scientific community, in addition to the results of the studies and the data collected, also biological samples in order to accelerate the achievement of cognitive and/or clinical results of particular relevance[38]. A good compromise, which does not solve all the difficulties encountered, but which, in my opinion, remains the best possible solution, in balancing the rights and the many interests at stake, is to encourage increasingly incisively the establishment of networks of certified public biobanks, regulated by specific procedures for the activities of acquisition, storage, access, use of the samples, and which provide for the transfer of samples to other locations only in exceptional cases. Examples of "good practices" in this sense are not lacking[39], even during the health emergency itself, as in the case of research aimed at studying the genetic variants associated with severe forms of Covid-19 which have preordained the custody of the acquired samples in a certified public biobank; if on the one hand only the DNA or RNA extracted from the samples was sent to external laboratories for genetic analysis, on the other, in accordance with the statements in the attached disclosures of the protocols, the sharing with the community of the results obtained and the data collected[40] was instead foreseen and promoted, subject to guarantees, by other researchers to restrict their use to the study of the causes and consequences of Covid-19.

[36] In today's disclosures there is always a supplement on privacy that refers to the provisions contained in the *Regulation (EU) 2016/679* and, as regards Italy, also to *the Legislative Decree 30 June 2003, n ° 196 Personal Data Protection Code, as amended by Legislative Decree 101/2018 and supplemented by the general authorisations of the Italian Data Protection Authority, for the processing of genetic data and the processing of personal data carried out for scientific research purposes* (see provision no.146 of 2019).

[37] In general, this is multicentre research promoted by large pharmaceutical companies, with offices and analysis laboratories located in other European and non-European countries.

[38] Cfr. L. PALAZZANI, *Informed consent in biomedical research in the pandemic context,* cit.

[39] The reference is to some multicenter studies reviewed by the Paediatric Ethics Committee for Clinical Trials of Tuscany.

[40] In the opinion of the ITALIAN COMMITTEE FOR BIOETHICS, *Biomedical research for novel therapeutic treatments within the Covid-19 pandemic: ethical issues*, cit., data are defined as "a valuable asset" for the advancement of knowledge and it is desirable for researchers to share (data sharing) at every level, also in order to avoid duplication or undersized research.

Special issue

How Spanish biobanks have adapted the informed consent process during the Covid-19 pandemic

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ABSTRACT: Due to the situation caused by the Covid-19 pandemic, biobanks have adapted, among other processes, the obtaining of informed consents (IC). This paper details the most relevant elements of the applicable regulations, describes the adaptations done by some of the biobanks of the Spanish Biobank Network to manage the IC process, which have been approved by their Ethics Committees, and draws some conclusions from the results obtained from the survey carried out on these biobanks.

KEYWORDS: Biobanks; bioethics; Covid-19; informed consent; Spain

SUMMARY: 1. Introduction – 1.1. The context of biobanks in Spain – 1.2. Key concepts relating to informed consent – 1.3. The management of informed consent according to Spanish legislation – 1.4. The position of the main international and national organizations on the informed consent process during the Covid-19 pandemic – 1.5. The importance of Ethics Committees for the approval of protocol changes – 2. Methodology – 3. Results and discussion – 4. Conclusions.

1. Introduction

On January 31, 2020, the World Health Organization (WHO) declared the outbreak of Covid-19 infection as a public health emergency of international importance, which they raised to an international pandemic on March 11, 2020. In Spain, this circumstance led to the establishment of a state of national alarm on two occasions, in accordance with the measures provided for in two Royal Decrees[1,2].

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[1] Real Decreto 463/2020, de 14 de marzo, por el que se declara el estado de alarma para la gestión de la situación de crisis sanitaria ocasionada por la infección Covid-19 (BOE no. 67, of March 14, 2020).

[2] Real Decreto 926/2020, de 25 de octubre, por el que se declara el estado de alarma para contener la propagación de infecciones causadas por el SARS-CoV-2 (BOE no. 282, of October 25, 2020).

The pandemic has generated a major health crisis due to the high number of infected people, who pose a risk to the health of the population as a whole, and due to the high number of people who need health care, and with relative frequency, hospitalization and critical care, leading to a saturation situation of hospital emergencies and Intensive Care Units. In order to mitigate this situation and reduce the risk of contagion of the disease, when the first state of alarm was decreed, extraordinary measures of different kinds were adopted and applied to the entire population and, in particular, to those affected. On the other hand, emergency measures were also established to face the economic and social impact of Covid-19, including measures to support research on the infection. Thus, the activity of biobanks has been intensified due to an increase in the number of requests for samples, specifically from Covid-19 infected subjects, for use in research projects on the disease. The adaptation of biobanks to this new reality depends, among other factors, on the following ones[3]:

- Human resources (on-site or remote work) and material resources (facilities, equipment and security measures) available.
- The biosecurity guidelines established by the institution to which they are attached.
- The degree of difficulty of obtaining informed consent (IC) by a healthcare staff swamped with a lot of work, taking into account that the usual procedure for obtaining IC involves the signature of the patient (or legal representative, if applicable) and the reporting staff (health professionals).
- The different sources of the samples (surplus / expressly collected samples).
- The quantity, variety and time of collection of the samples to be stored.

Under these circumstances, biobanks are facing, when managing samples from patients with Covid-19, with situations that require a rethinking of the system to be used for the inclusion of samples and obtaining the IC.

1.1. The context of biobanks in Spain

Before addressing this issue, it is worth explaining what biobanks are like in Spain, since their governance, organizational characteristics and sources of funding are different in each European country[4]. In the case of Spain, biobanks for biomedical research purposes are regulated by the *Ley 14/2007, de 4 de julio de investigación biomédica* and the *Real Decreto 1716/2011, de 18 de noviembre*, which develops the mentioned Law. Biobanks are part of the strategic agendas of the National Health System for the promotion and improvement of public and universal healthcare. In fact, the rules that regulate them highlight their "vocation of public service", although it also defines them as "public or private, non-profit establishments that host a collection of biological samples (of human origin) conceived for diagnostic or biomedical research purposes, and organized as a technical unit with quality, order and destination criteria"[5,6]. Thus, a biobank must have a defined structure, a

[3] Spanish Biobank Network, *Gestión por los biobancos de la Red Nacional de Biobancos de la obtención de los consentimientos informados ante la pandemia para investigación sobre el SARS-CoV-2 y la enfermedad Covid-19* (Comité Asesor Ético-Legal, April 2020).

[4] I. MEIJER, J. MOLAS-GALLART, P. MATTSSON, *Networked research infrastructures and their governance: The case of biobanking*, in *Science and Public Policy*, 39 (4), 2012, 491-499.

[5] Ley 14/2007, de 3 de julio, de Investigación biomédica (BOE no. 159, of July 4, 2007).

[6] Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras

scientific direction and a written operating regulation. As is logical, its main function is to provide quality samples to the scientific community.

These rules establish the authorization system for the constitution and operation of biobanks, which must be authorized by the Autonomous Communities and registered in the Spanish Biobank Register of the *Instituto de Salud Carlos III* (ISCIII). There are currently 75 biobanks authorized in Spain for biomedical research purposes.

The ISCIII, a Spanish organization of international reference in the field of Public Health and Biomedical Research, created, in 2009, the Spanish Biobank Network with the aim of providing high-level scientific, technical and technological support to R+D+i projects in science and health technologies, as well as encouraging innovation in health technologies, by supplying high-quality human biological samples and associated data.

During the last years, the efforts of this network, formed by 39 members, have focused on working in a coordinated but decentralized way, and on creating a catalogue of samples and a single window for sample requests. Although Spain is not a member of the European research infrastructure for biobanks BBMRI-ERIC (https://www.bbmri-eric.eu/), this organization has served as a model to define the work of Spanish biobanks and reconfigure their practices[7]. This fact confirms that, in the case of biobanks, governance tends to be based on guidelines and international collaboration, rather than on state or government action[8].

Since the beginning of the pandemic, the Spanish Biobank Network has played a key role in the coordination of national biobanks, by holding weekly informative meetings, preparing guides and recommendations for the management, collection and conservation of biobank samples from patients affected by Covid-19, to ensure their later usefulness both in terms of quality and integrity as well as the ethical-legal guarantee with respect to current regulations[3,9], and creating a national repository of clinical information associated with samples from patients affected by Covid-19 admitted at different stages of the disease. This information includes epidemiological and clinical aspects, biological markers, treatments and comorbidities, in short, data of interest for detailed knowledge of the characteristics of the patients.

Similar experiences are happening at the European and international level. The International Society for Biological and Environmental Repositories (ISBER) has fostered collaboration between countries to analyze the impact of the pandemic on biobanks globally, while the BBMRI-ERIC has organized two webinars that have helped to continuously monitor the evolution of the pandemic at the international level.

1.2. Key concepts relating to informed consent

The world is living in a reality in which it is necessary to establish a balance between reducing obstacles that appear during the conduct of an investigation, in search of efficiency in terms of time

biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica (BOE no. 290, of December 2, 2011).

[7] V. ARGUDO-PORTAL, M. DOMÈNECH, *The reconfiguration of biobanks in Europe under the BBMRI-ERIC framework: towards global sharing nodes?*, in *Life Sciences, Society and Policy,* 16:9, 2020.

[8] A.C. DA ROCHA, *Biobancos, cultura científica y ética de la investigación*, in *Dilemata*, 4, 2010, 1-14.

[9] Spanish Biobank Network, *Guía de la Red Nacional de Biobancos para el manejo de muestras humanas en investigación biomédica. Recomendaciones ante la pandemia de Covid-19* (April 2020).

and needs, and the guarantee of its methodological rigor. Depending on whether one or the other of these aspects is given more importance, four types of IC can be considered[10]:

- Specific/closed consent. The donor gives consent for a specific research project. Therefore, it is not possible to carry out secondary research derived from samples stored in biobanks, since at the time of donation there is no information on the future research in which the sample will be used. The solution would be to ask donors for new consent to use the sample previously stored in the biobank, although this can be annoying for them and ineffective for research, and end up causing a reduction in the number of available participants.
- Broad consent. The donor gives consent not only for specific studies, but also extends the acceptance to any class or line of research that the biobank deems appropriate. In this way, advances in research are facilitated.
- Blanket/open consent. The donor gives consent, without restrictions regarding the scope and duration of the research, for any future use of his biological sample and its associated clinical data, including forensic and commercial uses. This type of consent requires minimal administrative and organizational effort. It is used by most genetic data biobanks.
- Dynamic consent. This consent is based on the use of modern communication strategies (computer tools) to inform, involve, offer options and obtain consent for each of the research projects that may be derived from a biological sample. This is a model of continuous two-way communication between donors and researchers, thus overcoming the ethical problem that passive participation implies. It generates greater trust on the part of donors in the research, since participants have control over the use of their biological samples and associated clinical data.

Given these possibilities, it should be noted that there are two different approaches that guarantee the privacy of personal data associated with biological samples and with other relevant data from a public health point of view:

- Anonymization, or irreversible disassociation, which is defined as the "process by which it is no longer possible to establish by reasonable means the link between a piece of data (or a biological sample) and the subject to whom it refers" (art. 3.c) of the *Ley de Investigación biomédica*). This same law also defines, in art. 3.i), the anonymised or irreversibly disassociated data as that "data that cannot be associated to an identified or identifiable person as the nexus with all information that identified the subject has been destroyed or because such association demands a non-reasonable effort, understood as the use of disproportionate amounts of time, expense and work"[5].
- Pseudonymisation, or reversible disassociation, which is defined as that "processing of personal data in such a way that it can no longer be attributed to an interested party without using additional information, provided that said additional information appears separately and is subject to technical and organizational measures designed to guarantee that the personal data is not attributed to an identified or identifiable natural person" (art. 4.5 of Regulation (EU)

[10] N. SERRANO-DÍAZ, E. GUÍO-MAHECHA, M.C. PÁEZ-LEAL, *Consentimiento informado para Biobancos: Un debate abierto*, in *Revista de la Universidad Industrial de Santander. Salud*, 48(2), 2016, 246-256.

2016/679)[11]. This concept also appears in the *Ley de Investigación biomédica,* although with different terminology, since art. 3.k) defines the codified or reversibly disassociated data as that "data that is not associated to an identified or identifiable person as the information that identified that person has been substituted or detached using a code that allows the reverse operation"[5]. In simpler terms, pseudonymising consists of substituting one attribute for another in a record.

Thus, the anonymization can be considered absolute, since it is not possible to know, by reasonable means, the personal data that were originally processed. On the contrary, in the case of the pseudonymisation, the person responsible for the data could reverse the process in order to access the information subject to protection.
For all the above, it is recommended that the less restrictive the type of consent granted by donors is regarding the possible uses of the sample or the data, the greater security measures are used to preserve their identity.

1.3. The management of informed consent according to Spanish legislation

In Spain, the use of biological samples of human origin and associated data in biomedical research is currently regulated by three legal instruments[5,6,12] that include exceptional cases and special regimes that contemplate the adaptation of obtaining IC to the clinical situation of the subject, the pandemic situation and the need for research for public health reasons, and which have been taken into account to assess the situation in each biobank and decide how to proceed in this regard.
It is established that the "obtaining of biological samples for biomedical research shall be undertaken solely when the previous written consent has been obtained from the source subject". The requirements established by Spanish legislation for the generic IC model tallies with broad consent. This consent will also be essential when "the aim is to use biological samples for biological research that have already been obtained for a different purpose, irrespective of whether there is an anonymization"[5].
However, there are some exceptions to this obligation. "Codified or identified samples for biomedical research may be used without the consent of the source subject in situations of exceptional relevance and gravity for public health or when the obtaining of this consent is not possible or it entails a non-reasonable effort. In these cases, the favourable verdict of the corresponding Research Ethics Committee (REC) shall be necessary, which must take into account, at least, the following requisites[5,6]:

a) That the research is of general interest.
b) That the research is undertaken by the same institution that requested the consent for the obtaining of samples, if such consent is necessary.

[11] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Official Journal of the European Union L 119, 4.5.2016).
[12] Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales (BOE no. 294, of December 6, 2018).

c) That the research is less effective or not possible without the identifying data of the source subject.
d) That there is no record of an express objection of the source subject.
e) That personal data is guaranteed confidentiality.
f) That there is no viable alternative to carry out the project with another group of samples for which consent is available."

Moreover, the *Ley Orgánica 3/2018, de Protección de Datos* adds that "health authorities and public institutions with powers in public health surveillance may carry out scientific studies without the consent of those affected in situations of exceptional relevance and severity for the public health". On the other hand, if the study is carried out by a research group, the consent of the subject for the secondary use of the data (study related to the initial research) can be dispensed with when the following conditions are met[12]:

- The data is pseudonymised.
- There is express authorization from the corresponding REC.

The Spanish legislation also regulates other aspects related to the management of IC by biobanks:

- Time of signing the consent (art. 60.1 and 60.2 of the *Ley de investigación biomédica* and art. 23.4 of the *Real Decreto 1716/2011*)
- Information prior to consent (art. 59 of the *Ley de investigación biomédica* and art. 23.2 and 23.3 of the *Real Decreto 1716/2011*)
- Confidentiality of the source subject (art. 59.1.h) of the *Ley de investigación biomédica*, additional provision 17.2.d) of the *Ley Orgánica 3/2018, de Protección de Datos* and art. 34.3 of the *Real Decreto 1716/2011*)
- Possible purposes of obtaining samples (art. 22.2 of the *Real Decreto 1716/2011*)
- Final destination of non-biobank samples (arts. 59.1.f) and 61.1 of the *Ley de investigación biomédica* and art. 27 of the *Real Decreto 1716/2011*)
- Use of samples from certain groups (art. 58.5 of the *Ley de investigación biomédica* and arts. 23.2.n) and 26.1 of the *Real Decreto 1716/2011*)
- Use of samples from other countries (art. 31 of the *Real Decreto 1716/2011*)

1.4. The position of the main international and national organizations on the informed consent process during the COVID-19 pandemic

In clinical practice, there may be situations in which it is not possible to obtain IC by the usual means and it must be requested by other means, such as orally, or even the need for the exemption of obtaining it should be considered. In fact, as early as 1964, the Declaration of Helsinki of the World Medical Association provided that, in the case of exceptional situations in which it is impossible or impractical to obtain consent for a research, it can only be carried out after being considered and approved by a REC[13].

[13] WMA, Declaration of Helsinki – Ethical Principles for Medical Research involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964.

The International Bioethics Committee (IBC) has indicated that, although the secondary use of health data requires a new specific consent, such rule finds an exception when procedures such as pseudonymisation are implemented, which prevents researchers or third parties from accessing personal data[14]. Another four requirements are added to this one (apparent public interest in the research; difficulty in obtaining a new consent; legal origin of the data; and evaluation by a REC).

The pandemic has highlighted the need to find choices to the usual ethical review procedures. In the current context, the Pan American Health Organization and the World Health Organization itself encourage the practice of broad consent for the use of samples and data in future research that is not planned yet but will probably be designed as new information emerges[15].

Along the same lines, the Bioethics Committee of Spain, in an emergency such as the current one, recommends authorizing the secondary use of health data and biological samples without requiring a new express consent from the source subjects or, in the case of deceased people, their legal representatives. It also emphasizes that the data and samples from health centers that have taken part in the treatment of patients infected with the SARS-CoV-2 virus should be considered, in general, of legal origin, as it is understood that the patients have given their consent to the treatment or any of the exceptions to consent provided by law has occurred[16]. In addition, it indicates that, for this secondary use without express consent to be reasonable, it must have a very relevant interest for the health of the community and enough guarantees must be implemented to prevent non-legitimized third parties from accessing the individual's identity through the data. As expressed above, this can be achieved through two different approaches: anonymization and pseudonymisation. The authorization of the corresponding REC is also necessary, as established in the additional provision 17.2 of the *Ley Orgánica 3/2018, de Protección de Datos*. The Bioethics Committee of Spain makes all these recommendations based on the legal regime applicable to these cases, which it explains in depth in section 3 of its report.

On the other hand, and although it does not directly affect the field of biobanks, the approach of the European Medicines Agency regarding the management of ICs for clinical trials during the pandemic is also relevant. This body has stated that "unless linked to the implementation of urgent safety measures, changes in IC procedures will need to be reviewed and approved by the relevant ethics committee in advance", and that "in case a sponsor plans to initiate a trial aiming to test new treatments for Covid-19, advice should be sought on alternative procedures to obtain IC, in case the physical consent cannot leave the isolation room, and therefore is not appropriate as trial documentation"[17]. And it adds that "if re-consent is necessary for the implementation of new urgent changes in trial conduct, alternative ways of obtaining such re-consent should be considered during the pandemic. These could comprise contacting the trial participants via phone or video-calls and

[14] International Bioethics Committee, UNESCO, *Report Of The IBC On Big Data And Health* (Paris, 15 September 2017).

[15] Pan American Health Organization (World Health Organization, Regional Office For The Americas), *Ethics guidance on issues raised by the novel coronavirus disease (Covid-19) pandemic* (Washington, D.C., March 16, 2020).

[16] *Informe del Comité de Bioética de España sobre los requisitos ético-legales en la investigación con datos de salud y muestras biológicas en el marco de la pandemia de Covid-19* (Madrid. April 28, 2020).

[17] European Medicines Agency, *Guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic* (Version 3, 28/04/2020).

obtaining oral consents, to be documented in the trial participants' medical records, supplemented with e-mail confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants are back at the regular sites".

1.5. The importance of Ethics Committees for the approval of protocol changes

There is no single method that all Spanish biobanks can apply, it is difficult to establish a harmonized procedure for all of them. In any case, changes in the management of obtaining ICs must be endorsed by the opinion of the Ethics Committee to which the biobanks are attached (REC), which makes an assessment, taking into account the following aspects[3]:

- The implementing legislation. Apart from the three previously mentioned legal texts of state scope, it should be noted that, during the first state of alarm caused by Covid-19, only one of the seventeen autonomous communities that make up the country (Galicia) has specifically regulated the management of IC by biobanks during the health emergency period[18].
- The urgency of availability of samples for projects on Covid-19.
- The circumstances of each biobank.
- The inability of obtaining IC in a hospital by non-health staff.
- The infectious capacity of the physical IC document.
- The isolation of the admitted subjects and the severity of their condition, which affects their ability to consent.

Taking into account all these factors, RECs can choose from different decisions, ranging from authorizing total exemption from obtaining the IC to forcing consent to be obtained through the usual procedure, including intermediate options such as obtaining the IC in the near future or authorization of oral consent or in electronic format.
The role of the RECs is also essential in evaluating the requests for samples received by biobanks and the methodological, ethical and legal quality of research projects. This process is a new point of control and verification of compliance with the procedure that had been established to obtain ICs, always trying to guarantee respect for the fundamental rights of people, also and, specially, in times of health emergency[19].

2. Methodology

In order to better understand how the management of ICs by Spanish biobanks has worked since the Covid-19 pandemic began, an online survey (Annex) was carried out, the preparation of which was based, among other sources, in a report published by the Spanish Biobank Network in April 2020. The survey was sent to 43 biobanks from the coordination office of the network itself, a large majority of

[18] Orden de 2 de abril de 2020 por la que se aprueban medidas en materia de investigación sanitaria en los centros del Sistema público de salud de Galicia durante el período que dure la emergencia sanitaria por el COVID-19 (Diario Oficial de Galicia no. 68, of April 7, 2020).
[19] A. Cervera Barajas, M. Saldaña Valderas, *Investigación clínica y consentimiento informado en época de pandemia COVID-19. Una visión desde la ética de la investigación*, in *Medicina Clínica*, 2020.

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them being members of it. According to the Spanish Biobank Register, there are 75 biobanks authorized to act as such in Spain[20], so the number of biobanks to be surveyed represents a sufficiently representative sample to draw conclusions.
Although participation in the survey was voluntary, a thank you message was sent to all those biobanks that offered their collaboration. Biobanks had 9 calendar days (from March 8 to March 16, 2021) to answer the 13 questions posed in the survey.
At the beginning of the survey, the identification of the biobank that responded was requested. This request was made to check that a single answer had been obtained for each biobank. The scientific directors of the biobanks were informed of this point and warned that the data obtained would be published, in any case, anonymously and in an aggregate manner. The survey contained two filter questions (see survey in Annex):

- Question 2. If "No" was answered, the survey ended at that point;
- Question 7. If the answer was "Yes", then another question included in question 7 itself would appear. If the answer was "No", you would advance directly to question 8.

3. Results and discussion

Finally, the survey was answered by 36 of the 43 biobanks to which it was sent, which represents a participation rate of 84%. Considering that there are 75 authorized biobanks in Spain, the study includes information on almost 50% of the authorized Spanish biobanks. The biobanks that have participated in the survey come from the following autonomous communities: Aragón, Asturias, Balearic Islands, Basque Country, Cantabria, Castilla y León, Catalonia, Community of Madrid, Galicia, Murcia, Navarra and Valencian Community.
91.7% of the total number of biobanks that responded to the survey have managed samples for projects or created a collection of patients affected by Covid-19 in the course of the pandemic, and 75% have modified the procedure of obtaining IC, which involves its signature by the patient (or the legal representative) and the reporting staff.
Considering that the rest of the questions in the survey have focused on the modifications carried out in the way of managing IC, the results presented below correspond to a total of 27 biobanks. The remaining 25% did not answer any more questions in the survey.
It is especially striking that, among the 25% of the biobanks that did not modify the usual procedure for obtaining IC, there are several biobanks from hospitals in the Community of Madrid, the autonomous region most affected by the pandemic during the first of the two states of alarm.

Statistical analysis of the biobanks that were forced to modify the procedure for obtaining IC

One aspect that has been asked about has been the dates during which biobanks have been affected in obtaining the IC of Covid-19 patients, considering two different periods:

[20] https://biobancos.isciii.es/ListadoBiobancos.aspx (last visited 11/03/2021).

- First state of alarm caused by the Covid-19 disease (from March 14 to June 21, 2020). During this period, 17 of the 27 biobanks whose way of obtaining IC was affected did so from the week following the declaration of the state of alarm, which reflects the speed of action. This situation lasted until June 21 in 26 of the 27 biobanks.
- From the end of the first state of alarm to the start date of the survey. During this period, almost 90% of these 27 biobanks had their way of obtaining IC affected. This situation began on the same day as the end of the first state of alarm (June 22, 2020) for 75% of them. On the other hand, for 66% of biobanks, this situation lasted until the start date of the survey, that is, it was still in force at that time.

Regarding the Covid-19 patient samples managed by the biobanks, 25.9% of them have worked only with surplus healthcare samples, 11.1% have worked only with expressly collected samples, and the remaining 63% have worked with both types of sample.
In Figure 1, you can see how the management of IC has changed in biobanks for the case of patients diagnosed with Covid-19. These data are closely related to those obtained in question 12, which can be seen in Figure 2. The alternatives to the standard obtaining of the IC have been based mainly on allowing the exemption of its obtaining or the verbal consent.

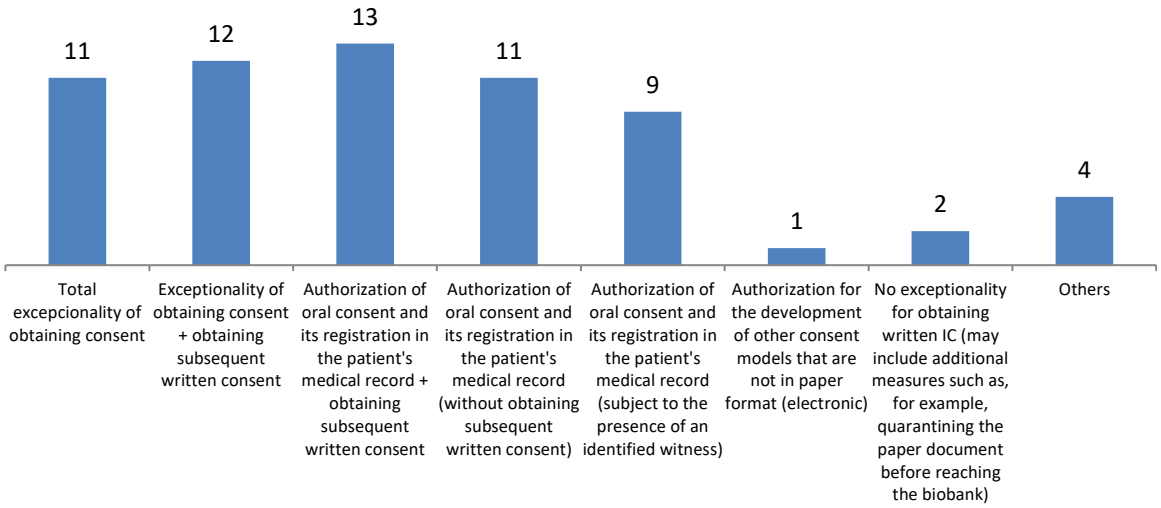

Figure 1. Measurement of the frequency in the application of several action choices regarding obtaining the IC of COVID-19 patients in Spanish biobanks (The same biobank may have applied more than one option)

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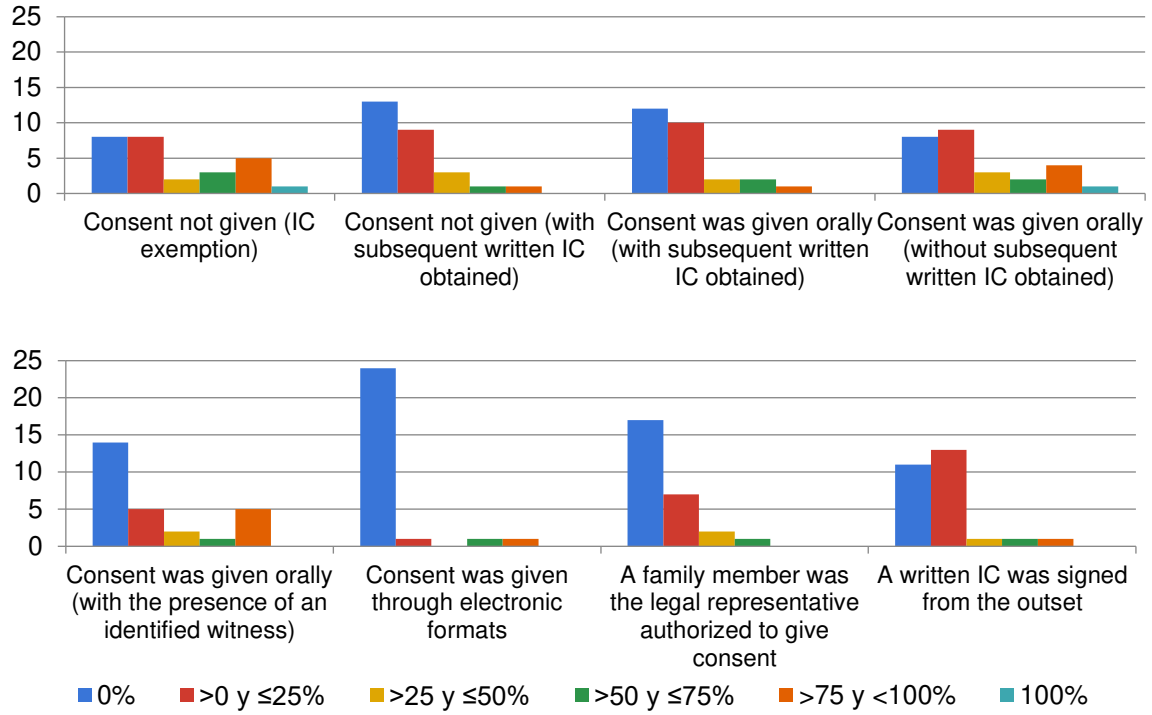

Figure 2. Estimation of the percentage of people who are in different situations related to IC with respect to the total number of people from whom a COVID-19 sample was obtained for biobank (The ordinate axis represents the number of biobanks that chose each percentage section as a response)

Regarding the people who did not sign the written IC from the outset, the process to collect that document in paper format is active in 44.4% of the biobanks (dated March 8, 2021), while in the rest is not active because it has not started (25.9%), has already finished (3.7%) or is not applicable (25.9%). In the cases in which the process is underway, the average percentage of people from whom the document has already been obtained is 45.7%.

For 51.9% of biobanks, the new way of IC management has undergone a modification again. Table 1 shows which have been both the most common previous and later options with respect to this modification. In this case, modification should be understood as the verdict of a REC. Therefore, the previous options are those allowed by the REC before the verdict, and the later options are those allowed by the REC after the verdict. It should be noted that neither the previous nor the later options contemplate obtaining IC through the usual procedure as the only possibility allowed.

	Previous option	Later option
Total exceptionality of obtaining consent	9	3
Exceptionality of obtaining consent + obtaining subsequent written consent	9	9
Authorization of oral consent and its registration in the patient's medical record + obtaining subsequent written consent	9	8
Authorization of oral consent and its registration in the patient's medical record (without obtaining subsequent written consent)	8	6

Authorization of oral consent and its registration in the patient's medical record (subject to the presence of an identified witness)	3	4
Authorization for the development of other consent models that are not in paper format (electronic)	1	2
Authorization of the consent given by the patient's relatives + subsequent consent of the patient	2	2
No exceptionality for obtaining written IC (may include additional measures such as, for example, quarantining the paper document before reaching the biobank)	1	2
Others	1	0

Table 1. Number of biobanks whose RECs chose different choices in terms of obtaining the IC of COVID-19 patients as previous and/or later options regarding a change in the way of proceeding during the time in which the obtaining was not carried out by the usual method (14 biobanks have participated in these statistics)

Regarding the verdict of exceptionality, without being the options raised in question 8 mutually exclusive, 70.4% of the biobanks have affirmed that it was requested by themselves, while 22.2% recognized that it was requested by research groups of their center whose samples were prepared in the biobank. On the other hand, 29.6% of the biobanks admit that the verdict was issued by their REC without previous request.

These verdicts could have been motivated by the existence of other previous documents. Table 2 shows the influence of several reports or legislation on the verdicts of the RECs:

Autonomous (regional) legislation (decree, order ...)	6
Verdict/recommendation of a Reference Committee	8
AEPD (Spanish Agency for Data Protection) report on data processing in relation to COVID-19	8
Bioethics Committee of Spain report on the ethical-legal requirements in research with health data and biological samples in the framework of the COVID-19 pandemic	8
Document prepared by the Spanish Biobank Network "Management of obtaining ICs by the biobanks of the Spanish Biobank Network in the face of the pandemic for research on SARS-CoV-2 and the COVID-19 disease"	11
None of these options	6

Table 2. Measurement of the influence that the publication of different documents has had on the REC's verdicts of exceptionality (The numbers indicate how many biobank RECs relied on each document for the preparation of the verdict. Each biobank has been able to choose more than one option)

It should be noted that two of the responses that marked the option "None of these options" (Table 2) did so because the information for which it is asked was unknown in the biobank, referring to the REC to which they are assigned as responsible of the decision. In only 3.7% of the biobanks, the verdict of exceptionality was applied to all their active collections, while in 85.2% it was applied to the collections of patients affected by Covid-19. In addition, in 25.9% of the biobanks the verdict was applied to the Covid-19 patient samples prepared in the biobank and linked to research projects.

On the other hand, it should be noted that, in at least one in three centers, the verdict of exceptionality has not been applied equally to biobank samples than to samples linked to research projects on Covid-19 (however, it is necessary to indicate that half of the respondents do not know if it has been applied equally or not, so it is possible that the real data is much higher than that which

has been reviewed). Some of the differences that have been recorded in the survey in this regard are:

- "Total exceptionality of consent in research projects, although with anonymization obligation";
- "Absence of verdict for samples destined to projects";
- "Absence of written consent in the case of the biobank, and written consent signed by a witness in the case of the project";
- "Samples of non-Covid-19 patients collected with the usual consent".

4. Conclusions

Different conclusions can be drawn from the results obtained in the survey. First of all, it is evident that a large majority of Spanish biobanks have managed Covid-19 patient samples. Thus, it is clear that the activity of these research facilities has been altered by the pandemic, as has happened in all areas of the Spanish health system.

It has also been reflected in the results that this management of Covid-19 patient samples has caused an alteration in the usual way of obtaining IC in the case of most biobanks. Although this alteration was very frequent during the first state of alarm, it has continued to be present, albeit with a slightly lower frequency, in subsequent months. So much so that, in March 2021, approximately half of the biobanks that have managed Covid-19 patient samples (17 out of 33 biobanks) have not yet recovered the usual procedure for obtaining consent.

About 90% of the biobanks that have managed this type of sample have received surplus healthcare samples, which confirms that they have faced difficulties in obtaining IC through the usual course. The vast majority of RECs have made decisions so that biobanks could adapt to this situation. The most widespread response among RECs has been to allow exemption in obtaining consent or authorization of oral consent, subject, in both cases, to obtaining written consent at a future time when conditions are more favourable. For this reason, 70% of biobanks are currently collecting these documents or pending to start collecting them. On the contrary, the authorizations of electronic formats of consent or of relatives as legal representatives have been little-explored options.

It should be remembered that obtaining the IC in a future time under more favourable conditions is not compulsory when the use of the samples and data has been carried out in the framework of a public health emergency, as explained above. However, it can be a guideline made by a REC, which should not be understood as a legal obligation, but a moral one. Therefore, a refusal by the patient to consent to this retrospective use would not imply a legal problem, and it would even be possible to continue using said data if it is considered essential, usually on the condition that they are subjected to an anonymization process (or, in other words, an irreversible disassociation).

Notwithstanding the above, for half of the biobanks, the verdicts of the RECs for the transfer of samples from biobanks to research projects have undergone modifications during the course of the pandemic. In this sense, it should be noted that the total exceptionality of consent (that is, without the obligation to obtain it in the future) was an option that was frequently allowed at the beginning of the pandemic but that has no longer been allowed so assiduously in later months, perhaps because the health emergency (volume of work in hospitals, need for research samples) decreased

its level of severity. This is a clear indication of the fair balance that has been attempted to be maintained between the rights of the individual and the benefit of the collective.

In one out of every three cases, the verdict of exceptionality was issued by the REC by its own initiative. This means that, in most cases, it was the hospital's own biobank or research groups who asked the RECs for an exceptionality. It is worth highlighting the uniformity of action in those Autonomous Communities that have a Reference Ethics Committee or a single REC compared to those in which each center has its own.

Furthermore, the report that most influenced the verdicts of the RECs was the one prepared by the Spanish Biobank Network[3], which is a symptom of the importance of this Research Platform as a benchmark for the biobanks of the country. However, this document already included, at the time of its publication, the verdicts available from some RECs in relation to the management of Covid-19 patient samples by biobanks. Although only one Autonomous Community urgently published specific legislation, it can be said that it was the fastest and most effective action.

In general terms, the data show that the use of samples in research projects on Covid-19 has suffered more restrictions than the inclusion of this type of samples in biobanks. This circumstance is in line with Spanish legislation, which establishes that, while health authorities can carry out studies without IC of those affected in particularly serious situations, IC can only be dispensed with for secondary use of these data and samples by a research group when they have been pseudonymised and there is a favourable verdict of a REC[12].

It is also important to note that, in only one of the 27 biobanks, the verdict of exceptionality was applied for all types of active collections, in addition to the Covid-19 collection. This fact implies a high degree of compliance with the law, which indicates that written IC can only be dispensed with in cases of "general interest" or for public health reasons. In other words, the health emergency was not a sufficient reason for the exceptionality to become a generalized method. Thus, in most biobanks, the IC for sample types already collected before the onset of the pandemic continued to be obtained by the standard procedure. This is a significant fact of the legal and ethical rigor with which the RECs acted and that the exceptions to the general rule should be well justified.

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ANNEX

SURVEY ON INFORMED CONSENT (IC) MANAGEMENT DURING THE PANDEMIC

***Mandatory**

Biobank name (The biobank name is a field that will be kept confidential and is only collected to ensure that only one survey per biobank is answered)*:

Autonomous Community to which the biobank belongs*:

1. Has your biobank managed samples for projects or created any collections of patients affected by COVID-19 during the pandemic?*
   - ☐ Yes
   - ☐ No

2. Has the obtaining of IC been affected at any time and cannot be carried out by the usual procedure that involves signing it by the patient/legal representative and the reporting staff?*
   - ☐ Yes
   - ☐ No

(If you answer "No" in question 2, the survey ends and is sent. If you answer "Yes", you continue to answer the following questions)

3. Taking into account only the period that includes the initial state of alarm (from March 14 to June 21, 2020), could you indicate the dates between which obtaining the IC of COVID-19 patients has been affected? (Please answer this question only if applicable to you)

   From _____ to _____
   (Dates are chosen from a drop-down calendar)

4. Taking into account only the period from the end of the initial state of alarm (June 21, 2020) to the present, could you indicate the dates between which obtaining the IC of COVID-19 patients has been affected? (Please answer this question only if applicable to you)

   From _____ to _____
   (Dates are chosen from a drop-down calendar)

5. The COVID-19 patient samples managed by the biobank are (You can indicate more than one option)*:
   - ☐ Surplus of healthcare samples
   - ☐ Expressly collected samples

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6. In what terms has obtaining the IC of COVID-19 patients been affected? (You can indicate more than one option)*
   - ☐ Total exceptionality of obtaining consent
   - ☐ Exceptionality of obtaining consent + obtaining subsequent written consent
   - ☐ Authorization of oral consent and its registration in the patient's medical record + obtaining subsequent written consent
   - ☐ Authorization of oral consent and its registration in the patient's medical record (without obtaining subsequent written consent)
   - ☐ Authorization of oral consent and its registration in the patient's medical record (subject to the presence of an identified witness)
   - ☐ Authorization for the development of other consent models that are not in paper format (electronic)
   - ☐ No exceptionality for obtaining written IC (may include additional measures such as, for example, quarantining the paper document before reaching the biobank)
   - ☐ Others. Indicate: _____

7. Has the way of obtaining consent undergone changes during the time that it has not been carried out by the usual procedure?*
   - ☐ Yes
   - ☐ No

(If you answer "Yes" in question 7, you continue to answer what is asked in this same question. If you answer "No", you go directly to question 8)

Indicate from which previous option to which later option the biobank has switched to (You can indicate more than one option):

Previous options:

- ☐ Total exceptionality of obtaining consent
- ☐ Exceptionality of obtaining consent + obtaining subsequent written consent
- ☐ Authorization of oral consent and its registration in the patient's medical record + obtaining subsequent written consent
- ☐ Authorization of oral consent and its registration in the patient's medical record (without obtaining subsequent written consent)
- ☐ Authorization of oral consent and its registration in the patient's medical record (subject to the presence of an identified witness)
- ☐ Authorization for the development of other consent models that are not in paper format (electronic)
- ☐ Authorization of the consent given by the patient's relatives + consent of the subsequent patient
- ☐ No exceptionality for obtaining written IC (may include additional measures such as, for example, quarantining the paper document before reaching the biobank)
- ☐ Others. Indicate: _____

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Later options:

- ☐ Total exceptionality of obtaining consent
- ☐ Exceptionality of obtaining consent + obtaining subsequent written consent
- ☐ Authorization of oral consent and its registration in the patient's medical record + obtaining subsequent written consent
- ☐ Authorization of oral consent and its registration in the patient's medical record (without obtaining subsequent written consent)
- ☐ Authorization of oral consent and its registration in the patient's medical record (subject to the presence of an identified witness)
- ☐ Authorization for the development of other consent models that are not in paper format (electronic)
- ☐ Authorization of the consent given by the patient's relatives + consent of the subsequent patient
- ☐ No exceptionality for obtaining written IC (may include additional measures such as, for example, quarantining the paper document before reaching the biobank)
- ☐ Others. Indicate: _____

8. The verdict of exceptionality ... (You can indicate more than one option)*:
   - ☐ was requested from the biobank itself.
   - ☐ was requested by research groups of my center whose samples were prepared in the biobank
   - ☐ was issued by the Research Ethics Committee (REC) to which the biobank is attached, without previous request.

9. The verdict of exceptionality was supported… (You can indicate more than one option)*:
   - ☐ by the publication of autonomous (regional) legislation (decree, order...).
   - ☐ by a verdict/recommendation of a Reference Committee
   - ☐ by the AEPD (Spanish Agency for Data Protection) report on data processing in relation to COVID-19 (https://www.aepd.es/es/documento/2020-0017.pdf)
   - ☐ by the Bioethics Committee of Spain report on the ethical-legal requirements in research with health data and biological samples in the framework of the COVID-19 pandemic (http://assets.comitedebioetica.es/files/documentacion/Informe%20CBE%20investigacion%20COVID-19.pdf)
   - ☐ by the document prepared by the Spanish Biobank Network "Management of obtaining ICs by the biobanks of the Spanish Biobank Network in the face of the pandemic for research on SARS-CoV-2 and the COVID-19 disease" (https://redbiobancos.es/wp-content/uploads/DT-PS-0002-Informe-Gestion-Consentimiento-Informado-COVID-19.pdf)
   - ☐ It was not motivated by any of these options

10. The verdict of exceptionality was applied… (You can indicate more than one option)*:
    - ☐ to all the active collections of the biobank
    - ☐ to the biobank's COVID-19 patient collections
    - ☐ to COVID-19 patient samples prepared in biobank and linked to research projects
    - ☐ Others. Indicate: _____

11. Has the verdict of exceptionality in your center been applied equally to biobank samples as to samples linked to research projects on COVID-19?*
    - ☐ Yes
    - ☐ No
    - ☐ I don't know

    If not, could you explain the differences? _____

12. During the states of exceptionality adopted by your REC and up to the present time, taking into account the people from whom a COVID-19 sample was obtained for your biobank, what percentage of them do you think...* (Mark only one percentage for each question)

	0%	>0 and ≤25%	>25 and ≤50%	>50 and ≤75%	>75 and <100%	100%
…did not give their consent (IC exemption)?						
…did not give their consent (with obtaining subsequent written IC)?						
…gave their consent orally (with subsequent obtaining of written IC)?						
…gave their consent orally (without subsequent obtaining of written IC)?						
…gave their consent orally (with the presence of an identified witness)?						
…gave their consent through electronic formats?						
…had a relative who was the legal representative authorized to give consent?						
…signed a written IC from the outset?						

13. Regarding the people considered in the previous question who did not sign the written IC from the outset, is the process to collect their IC on paper active?*
    - ☐ Yes
    - ☐ No, it hasn't started
    - ☐ No, since it's already over
    - ☐ No, it does not apply to the particular case of my biobank

    If the answer is affirmative, indicate the approximate percentage of people from whom this document has already been obtained: _____

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Special issue

How Covid-19 unveils the blurred borderlines between research and clinical practice monitoring: the use case of data protection and consent

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ABSTRACT: In the EU, the race to find Covid-19 treatment solutions has been going hand in hand with the acceleration of authorisation procedures for medicines and medical devices, and regulatory actions to monitor promising off-label and compassionate uses. This arguably contributes to the ongoing blurring of the borderlines between research and clinical practice monitoring. This article aims to map the ethical and legal implications of this trend for data protection and informed consent in pre-marketing and post-marketing studies on medicines and medical devices in the context of the Covid-19 public health emergency.

KEYWORDS: Clinical trial regulation; Covid-19; Data protection; Informed consent; Pharmaceutical and medical device regulation

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1. Introduction

Due to its high transmissibility and its pathological symptomatology, Covid-19 has had a deep impact on health and economic systems all over the world[1]. Since the outbreak of the pandemic, finding ways to prevent or treat such disease has become a top priority for governments and the industry alike. This has prompted regulators to implement measures to speed up approval processes for Covid-19 medicines and medical devices[2], and the EU is certainly no exception[3]. This emergency regulatory approach allows for the development of innovative products (especially vaccines) at an unprecedented pace. Simultaneously, it contributes to the ongoing blurring of the borderlines between research and clinical practice monitoring, moving research (and its uncertainties) from pre-marketing clinical trials to post-marketing settings, with an increasing role for post-marketing (especially observational) studies in real-world data collection.

This article aims to map ethical and legal implications of this trend for data protection and informed consent in studies regarding anti-Covid-19 medicines with special albeit not exclusive reference to pre-marketing and medical devices. To this end, this article follows the following structure. First, it preliminarily outlines the EU regulatory framework governing research on medicines and medical devices, particularly clinical trials, post-marketing studies and observational studies. Against this backdrop, it describes the EU and national emergency regulatory responses to Covid-19 to foster research on medicines and medical devices. Furthermore, it identifies the main challenges to data protection and free and informed consent in the context of the Covid-19 pandemic. Finally, the conclusions sum up the results of our analysis and identify avenues of further research in the context of the Covid-19 public health emergency.

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[1] In general, see M. Nicola *et al.*, *The socio-economic implications of the coronavirus pandemic (COVID-19): A review*, in *International Journal of Surgery*, 78, 2020, 185-193. As for the impact of Covid-19 on healthcare systems, see Z. Wang, K. Tang, *Combating COVID-19: health equity matters*, in *Nat Med*, 26, 2020, 458, doi: 10.1038/s41591-020-0823-6; D.M. Mann, J. Chen, R. Chunara, P.A. Testa, O. Nov, *COVID-19 transforms health care through telemedicine: Evidence from the field*, in *Journal of the American Medical Informatics Association*, 27(7), 2020, 1132–1135, doi. 10.1093/jamia/ocaa072; B. Armocida *et al.*, *The Italian health system and the COVID-19 challenge*, in *Lancet*, 5(5), 2020, E253. As for the economic impact of Covid-19, see W. McKibbin, R. Fernando, *The economic impact of COVID-19*, in R. Baldwin, B. Weder (eds.), *Economics in the Time of COVID-19*, London, 2020, 45-51, available at: https://www.incae.edu/sites/default/files/covid-19.pdf#page=52 (last visited 14/4/2021).

[2] In general, see N. Lurie *et al.*, *Developing Covid-19 Vaccines at Pandemic Speed*, in *N Engl J Med*, 382, 2020, 1969-1973, doi: 10.1056/NEJMp2005630. For more details on the US response, see C. Cassidy, D. Dever, L. Stanbery *et al.*, *FDA efficiency for approval process of COVID-19 therapeutics*, in *Infect Agents Cancer*, 15, 2020, 73, doi: 10.1186/s13027-020-00338-z; A.S. Kesselheim *et al.*, *An Overview of Vaccine Development, Approval, And Regulation, With Implications For COVID-19*, in *Health Affairs*, 40(1), 2021, 25-32, doi: 10.1377/hlthaff.2020.01620.

[3] M. Cavaleri *et al.*, *The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines*, in *Lancet*, 397(10272), 2021, 355-357; A.G. Fraser, P. Szymański, E. Macintyre, M. Landray, *Regulating drugs, medical devices, and diagnostic tests in the European Union: early lessons from the COVID-19 pandemic?*, in *European heart journal*, 41/23, 2020, 2140-2144; H.G.T. Defendi, L. da Silva Madeira, S. Borschiver, *Analysis of the COVID-19 Vaccine Development Process: an Exploratory Study of Accelerating Factors and Innovative Environments*, in *J Pharm Innov*, 2021, doi: 10.1007/s12247-021-09535-8.

2. The EU regulatory framework for research on medicines and medical devices

In the EU, before marketing a medicinal product, a manufacturer must gather safety and effectiveness data in a series of experimental phases (Annex I, Directive 2001/83/EC). Regulators, at the request of the applicant, assess on such data the benefit-risk ratio of the product and, if this ratio is positive, release a marketing authorisation (MA) (Articles 6 *et seq*., Directive 2001/83/EC). After MA, companies and regulators are required to monitor the effects of the approved medicines in the real world (so-called pharmacovigilance; Article 101 *et seq*., Directive 2001/83/EC), e.g., through post-marketing studies (PASs). A similar logic applies to medical devices (MDs), although a proper MA procedure does not apply. This paragraph summarises the EU rules applicable to pre-marketing and post-marketing research concerning medicines and medical devices, setting the ground for the subsequent analysis.

2.1. Clinical trials

In the EU, Directive 2001/20/CE (Clinical Trial Directive, CTD) defines CTs as any investigation into the effects of an investigational medicine (Art. 2(a) CTD). The CTD requires sponsors to obtain an authorization from the Member State where the CT will be conducted (Art. 9(2) CTD). It also subjects CTs to Good Clinical Practice (GCP) (Arts. 1(4) CTD), reflecting basic ethical principles as informed consent, proportionality between expected risks and benefits, and independent ethical review, in line with the Nuremberg Code, the Helsinki Declaration, and the Oviedo Convention on Human Rights and Biomedicine.

The CTD's failure to facilitate multinational CTs led to the adoption of the CTR. Intended to replace the CTD and domestic implementations, the CTR entered into force on 16 June 2014 but will apply six months after the EU Clinical Trials Information System will have achieved full functionality (Arts. 82(3) and 99 CTR).[4] The CTR clarifies that, while clinical studies include any investigation into the effects of a medicinal product, CTs are clinical studies where «*the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects*» (Art. 2(2) CTR). Also, the CTR centralises the approval of multinational CTs via the EU portal mentioned above.

Therefore, EU law adopts a "segregationist" approach to the medical research-practice divide, under which the two are mutually exclusive[5]. While interventions aimed at increasing scientific knowledge

[4] According to EMA, the launch of the portal is planned for December 2021 (https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation, last visited 14/4/2021) .

[5] This approach is also reflected in the US Belmont Report, an international reference document on the distinction between research and practice (T.L. BEAUCHAMP, Y. SAGHAI, *The historical foundations of the research-practice distinction in bioethics*, in *Theor. Med. Bioeth*, 33(1), 2012, 45-56). For more details on the related debate, see T. BEAUCHAMP, *Why our conceptions of research and practice may not serve the best interest of patients and subjects*, in *J Int Med*, 269, 2011, 383–7; M.F. VERWEIJ, *Commentary: The distinction between research*

constitute medical research, interventions with mere therapeutic aims are clinical practice falling outside CT legislation. This is regardless of whether the intervention is standard or non-standard. This may result in the under-protection of patients receiving non-standard treatments[6]. In any case the possible informative asymmetry shall be covered through the informed consent procedure, that find application also for non-interventional studies.

2.2. Post-authorisation studies

While CTs are typically conducted in preparation for a MA application, they can also be conducted as PASs, after a MA is granted[7]. PASs include Post-authorization Safety Studies (PASSs) and Post-Authorisation Efficacy Studies (PAESs). PASSs aim to gather additional information on the safety and benefit-risk profile of a medicine (Art. 1(15), Directive 2001/83/EC). PASSs can either be CTs or NISs, voluntary or imposed. Imposed PASSs include studies that are a specific obligation for a MA granted based on fewer data than normally required or if new data emerges challenging the initial MA assessment.

Likewise, PAESs cover both CTs and NISs, and may be imposed if (a) a MA has been released based on data less complete than usually required, as in the case of Conditional Marketing Authorisation (CMA) (Art. 14(7) of Regulation (EC) No 726/2004), or (b) efficacy concerns can be resolved only after MA or previous efficacy evaluations should be revised in light of real-world data (Delegated Regulation (EU) No 357/2014). PASs should be registered in the EU PAS Register, where EMA publishes protocols, abstracts and final study reports (Commission Implementing Regulation (EU) No 520/2012).

Finally, it is worth noting that the incoming CTR introduces the notion of low-intervention CTs, i.e., CTs on the use of already authorized medicines (Art. 2(c) CTR). As such, they are poised to enrich the toolbox of PASs. Low-intervention CTs are subject to less stringent requirements. In particular, informed consent may be obtained by «*simplified means*» (Art. 30(3)(c) CTR). This means that informed consent is considered to be given if information about the CT is given to the potential subject and this latter does not object to participation (Art. 30(2) CTR). Also, the CT sponsor determines the «*extent and nature of the monitoring*» considering «*all characteristics of the clinical trial, including* […] *whether the clinical trial is a low-intervention clinical trial*» (Art. 48 CTR). Since low-intervention CTs concern already approved medicines, this latter provision may be interpreted as enabling sponsors to implement weaker forms of monitoring. However, if the CT involves an off-label use for which published evidence is unavailable, the usual requirements apply (Art. 2(c) CTR).

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and practice – a response to T. Beauchamp, in *Journal of Internal Medicine*, 269, 2011, 388-391, doi: 10.1111/j.1365-2796.2011.02350_2.x.

[6] This risk has been highlighted in the literature cited in the previous note and N.E. KASS *et al*., *The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight*, in *The Hastings Center Report*, 43(1), 2013, S4-S15; G. HELGESSON, *Can and should the research–therapy distinction be maintained? Reflections in the light of innovative last-resort treatment*, in *Research Ethics*, 15(2), 2019, 1-14. doi: 10.1177/1747016119835461.

[7] F. TUBACH, *Role of the Post-Marketing Authorisation Studies in Drug Risk Surveillance: Specifications and Methodologies*, in *Therapie*, 66(4), 2011, 355–362; T.J. GIEZEN, A.K. MANTEL-TEEUWISSE, S.M.J.M. STRAUS *et al*., *Evaluation of Post-Authorization Safety Studies in the First Cohort of EU Risk Management Plans at Time of Regulatory Approval*, in *Drug Safety* 32(12), 2009, 1175-1187.

Therefore, low-intervention CTs may overall contribute to further blurring the boundaries between research and practice, lowering the level of regulatory requirements in certain research contexts. This will likely have an impact in the context of conditional and accelerated authorisation procedures, where PASs are increasingly performed to complement and enrich products' data profiles.

2.3. Observational studies

As anticipated, the data supporting the MA of a medicine may also be complemented by the observation of its real-world effects. To this end, non-interventional studies (NISs) are performed. NISs do not interfere with the course of clinical practice and observe data collected from the real world (e.g., from patient registries)[8]. This is why NISs are also called observational studies. This is reflected in their CTD definition: «*the medicinal product is prescribed in the usual manner 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 separated from the decision to enrol the patient in the investigation. [NISs] do not apply additional diagnostic or monitoring procedures to patients and use epidemiological methods for the analysis of collected data*» (Art. 2(c) CTD). Conversely, the CTR defines NISs as any «*clinical study other than a* [CT]». EMA GVP Module VIII clarifies that NISs «*also include those involving primary data collection (e.g., prospective observational studies and registries in which the data collected derive from routine clinical care)*». However, NISs are left to the Member States, where regulations vary wildly[9]. This complicates multinational observational research[10], despite its increasing importance in real-world data collection in making informed decisions on a medicine's regulatory statues and healthcare strategies[11].

2.4. Medical device clinical evaluation

A similar logic applies to MDs. Regulation (EU) No 2017/745 (Medical Device Regulation, MDR) will become applicable on 26 May 2021 and replace Directive 93/42/EEC (Medical Device Directive, MDD)[12]. The MDR sets out distinct conformity assessment (CA) procedures for different MD classes, based on their risk level. Unlike the MDD, the MDR requires a Clinical Evaluation Report for all MD classes. Manufacturers can obtain a CE marking with clinical investigations (CIs, under Chapter VI and

[8] J.F. ALIDJANOV, K.G. NABER, A. PILATZ *et al.*, *Evaluation of the draft guidelines proposed by EMA and FDA for the clinical diagnosis of acute uncomplicated cystitis in women*, in *World J Urol*, 38, 2020, 63-72.

[9] I. RAMIREZ, *Navigating the maze of requirements for obtaining approval of non-interventional studies (NIS) in the European Union*, in *Ger Med Sci.*, 13, 2015, Doc21, doi: 10.3205/000225.

[10] Observational studies naturally interact with pharmacovigilance and data protection law. For more details on such aspects, see, respectively, S.E. GÜLMEZ, *The new pharmacovigilance legislation and impact on observational studies*, in *Marmara Pharmaceutical Journal*, 17, 2013, 61-64, doi: 10.12991/201317374; G.H.P. METNITZ *et al.*, *The General Data Protection Regulation and its effect on epidemiological and observational research*, in *The Lancet Respiratory Medicine*, 8(1), 2020, 23-24.

[11] F. CLAUDOT *et al.*, *Ethics and observational studies in medical research: various rules in a common framework*, in *International Journal of Epidemiology*, 38,(4), 2009, 1104–1108, doi: 10.1093/ije/dyp164.

[12] Regulation (EU) 2020/561 of the European Parliament and of the Council of 23 April 2020 amending Regulation (EU) 2017/745 on medical devices, as regards the dates of application of certain of its provisions.

Annex X MDR). CIs are subject to several European Commission implementing measures[13] and the standards ISO 14155-1:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice). This framework is similar to GCP, which subjects CIs to scientific principles on clinical data collection and human experimentation ethical standards. CIs may be randomized clinical trials or a different study types, if their validity is duly proved to NCAs. Alternatively, manufacturers can claim equivalence with another product (Art. 61(3)(a) MDR); yet the MDR requires more equivalence evidence than the MDD (§ 3(e), Annex XIV MDR). Thus, not only high-risk but also medium-risk MDs will likely require CIs. Finally, the MDR requires Post-Market Surveillance (PMS) and Post-Market Clinical Follow Up (PMCF) (Chapter VII and Annex IX MDR). In particular, PMCF studies aim to confirm the safety and performance data acquired in the pre-approval phase. They can be structured like pre-approval studies (Art 74 MDR).

3. Regulatory responses to the Covid-19 epidemic in the EU

In the face of the Covid-19 pandemic, the EU scientific community and pharmaceutical/MD industry have been striving to develop medicines, vaccines, and medical devices to prevent and treat Covid-19. This paragraph offers an overview of the regulatory responses implemented by the EU and national competent authorities (NCAs) to support these endeavours[14].

This overview suggests that the race to find Covid-19 treatment solutions in the EU is based on two main regulatory pillars: (i) accelerated authorisation procedures; (ii) recommendations concerning off-label uses of medicines approved for other indications and (iii) compassionate uses of investigational products. All three pillars have implication on both informed consent to trial/treatment and on personal data processing.

Such an impact is also related to the strategy chosen by regulators to promote forms of clinical practice monitoring. Indeed, given the EU "segregation" between research and practice (see above, paragraph 2.1), patients receiving non-standard therapies may theoretically be exposed to substantially experimental uncertainties outside the protections required for experimentations on humans. In other terms, accelerated procedures blur the borderlines between medical research and practice, and may result in the scientific uncertainties inherent in the lack of comprehensive data being transferred from pre-approval trials to clinical practice. This situation likely induced regulators to compensate the less complete data required to approve Covid-19 produces with strengthened clinical practice monitoring. It is worth noticing as well that many jurisdictions have introduced[15] or

[13] See https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_guidance_meddevs.pdf (last visited 14/4/2021). For further details on the role of such guidance under the incoming MDR, see B. WILKINSON, R. VAN BOXTEL, *The Medical Device Regulation of the European Union Intensifies Focus on Clinical Benefits of Devices*, in *Ther Innov Regul Sci*, 54, 2020, 613-617, doi: 10.1007/s43441-019-00094-2.

[14] See below paragraphs 3.1 to 3.4.

[15] For instance, France has limited the civil liability of physicians prescribing medicines off-label against Covid-19 (Arts. L.3131-3 e L.3131-20, *Code de la Santé Publique*, following *loi* 290/2020). Similar proposals are discussed in Italy (G. COMANDÉ, *La responsabilità sanitaria al tempo del Coronavirus...e dopo*, in *Danno e responsabilità*, 2020, 297). In the USA, several states introduced forms of criminal and civil liability immunity for healthcare institutions and providers (R.L. KLITZMAN, *Legal Immunity for Physicians During the COVID-19 Pandemic: Needs to Address Legal and Ethical Challenges*, in *Chest*, 158(4), 2020, 1343-1345, doi:

are evaluating the option to introduce liability shields for medical doctors and healthcare facilities during the pandemic, eventually weakening patients' toolbox in case of harm.

3.1. Acceleration of authorisation procedures

The European Medicines Agency (EMA) has strived to accelerate the development of anti-Covid-19 products. To promote evidence generation, EMA provided recommendations on clinical trials (CTs)[16] and observational studies of real-world data during the pandemic[17]. EMA also set up research networks to conduct observational post-authorisation safety studies (PASS)[18].

EMA has also combined Rolling Review (RR) and Conditional Marketing Authorisation (CMA) to accelerate the approval of several anti-Covid-19 vaccines[19]. With RR, EMA evaluates data as they emerge in the development process (usually, applicants submit all data in the marketing authorisation application)[20]. Conversely, CMA is an authorisation for medicines addressing unmet medical needs in emergencies declared by WHO or EU (Regulation (EC) No 507/2006). It is granted based on less comprehensive data than usually required if the benefit of the medicine's immediate availability outweighs the risk associated with incomplete data. CMA holders must subsequently collect additional data to confirm that the benefit-risk ratio is positive. Since this acceleration of approval procedures may result in experimental uncertainties being transferred to clinical practice, EMA set up a pharmacovigilance plan[21] for Covid-19 vaccines strengthening ordinary pharmacovigilance activities, e.g., requiring MAHs (Market Authorization Holders) to outline the post-authorisation safety follow-up in the Risk Management Plans[22] and submit EMA monthly summary safety reports besides regular periodic safety update reports[23].

10.1016/j.chest.2020.06.007). At the federal level, the Public Readiness and Emergency Preparedness Act also offers extensive liability immunity during public health emergencies (N. AL-AZRI, *Health Care Workers' Legal Liability and Immunity During the COVID-19 Pandemic*, in *Disaster Medicine and Public Health Preparedness*, 2020, 1-2, doi:10.1017/dmp.2020.449).

[16] EMA, *Guidance on the management of clinical trials during the Covid-19 (Coronavirus) pandemic*, Bruxelles, 4 February 2021, https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf (last visited 14/4/2021).

[17] A. POTTEGÅRD, X. KURZ, N. MOORE, C.F. CHRISTIANSEN, O. KLUNGEL, *Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic*, in *Pharmacoepidemiol Drug Saf*., 29, 2020, 825-831.

[18] EMA, *Pharmacovigilance Plan of the EU Regulatory Network for Covid-19*, EMA/333964/2020, 3-4. EMA also encouraged researchers to register observational studies in the EU electronic register of post-authorisation studies (EU PAS Register) and share protocols and reports (https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-vaccines-covid-19-post-authorisation, last visited 14/4/2021).

[19] *Pzifer*, *Moderna*, and *Astrazeneca*. See M. CAVALERI, H. ENZMANN, S. STRAUS, E. COOKE, *The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines*, in *Lancet*, 397/10272, 2021, 355-357.

[20] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-developers-companies/covid-19-guidance-assessment-marketing-authorisation (last visited 14/4/2021).

[21] EMA, *Pharmacovigilance Plan of the EU Regulatory Network for Covid-19*, cit.

[22] EMA, *Pharmacovigilance Plan of the EU Regulatory Network for Covid-19*, cit., 3.

[23] Id.

However, there is no explicit obligation to inform patients about the conditional nature of the product's authorisation, also for the purposes of informed consent acquisition. This is a significant weakness of the emergency system, in which patients exposed to additional uncertainties should be made fully aware of this and give a specific consent.

3.2.. Off-label and compassionate uses

In lack of approved alternatives, physicians have been trying to treat Covid-19 patients with medicines approved for other conditions since the beginning of the Covid-19 outbreak [24]. While such 'off-label' prescriptions[25] offer promising therapeutic opportunities, they may practically expose patients to experimental risks since they have not been thoroughly studied and validated[26]. This grey area between clinical research and practice has caught the attention of EMA, which has released several recommendations[27].

Compassionate use programs (CUPs)[28] are another area blurring clinical research and practice in which EMA has provided guidance. Under Article 83, Regulation (EC) 726/2004, Member States set up CUPs to grant access to experimental medicines to patients unable to join RTCs and suffering from severe diseases that cannot be treated with authorised medicines[29]. EMA provided recommendations to favour a common approach in the EU and has released recommendations concerning potential Covid-19 treatments[30]. Finally, it is worth noting that the EMA's recommendations on off-label and compassionate use do not include specific information and consent provisions explicitly requiring to disclose the unauthorised nature of the prescription to patients.

3.3. Personal protective equipment and medical devices

The Covid-19 epidemic made the demand for personal protective equipment (PPE) and (MDs) skyrocket, including face masks, disinfectants, and ventilators. Therefore, the European Commission

[24] A. Shojaei, P. Salari, *COVID-19 and off label use of drugs: an ethical viewpoint*, in *DARU J Pharm Sci*, 28, 2020, 789-793; J.D. Alpern, E. Gertner, *Off-Label Therapies for COVID-19—Are We All In This Together?*, in *Clin. Pharmacol. Ther.*, 108, 2020, 182-184, doi: 10.1002/cpt.1862.

[25] In general, see European Commission, *Study on off-label use of medicinal products in the European Union*, Bruxelles, 2017, 7. On the civil liability implications of off-label prescribing, see A. Parziale, *Responsabilità civile da usi off-label di farmaci nell'UE: una prospettiva precauzionale*, in *Opinio Juris in Comparatione*, I(1), 2020, 11-29;; M. Di Paolo, B. Guidi, L. Nocco, *La prescrizione off-label: dentro o fuori la norma?*, in *Resp. Civ. Prev.*, 2010, 2165; F. Massimino, *La prescrizione dei farmaci «off label»: adempimenti, obblighi e responsabilità del medico*, in *Danno e Resp.*, 2003, 925.

[26] European Commission, *Study on off-label use of medicinal products in the European Union*, cit., cit., 112.

[27] E.g., see EMA, *COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine*, EMA/202483/2020 Rev.; EMA, *EMA gives advice on the use of non-steroidal antiinflammatories for COVID-19*, EMA/136850/2020.

[28] In general, see G. Balasubramanian *et al.*, *An overview of Compassionate Use Programs in the European Union member states*, in *Intractable & Rare Diseases Research*, 5(4), 2016, 244-254, doi: 10.5582/irdr.2016.01054; H. Sou, *EU Compassionate Use Programmes (CUPs)*, in *Pharm Med*, 24, 2010, 223-229.

[29] See below paragraph 3.4.

[30] E.g., see EMA, *EMA provides recommendations on compassionate use of remdesivir for COVID-19*, EMA/152575/2020.

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has recommended the use of all the measures available to expand the supply (Article 1, Commission Recommendation (EU) 2020/403). In particular, Member States should consider authorising derogations from conformity assessment procedures under Articles 11(13), Directive 93/42/EEC and 59, Regulation (EU) 2017/745 (Article 5 of the Recommendation). Also, market surveillance authorities may authorise the marketing of PPE and MDs ensuring an adequate level of health and safety according to the relevant regulations before conformity assessment is finalised, for a limited time and while the necessary procedures are finalised (Article 7 of the Recommendation). This means that, once a market surveillance authority confirms that a MD is compliant, the first batch of products may be marketed, although it does not bear the CE marking. Finally, the European Commission has provided practical guidance on PPE, disinfectants, and 3D-printed MDs[31]. As in the case of CMA, there is, however, no explicit obligation to disclose to patients that a MD has been marketed based on a less comprehensive assessment.

3.4. National policies

EU Member States have generally acted to accelerate approval procedures for the protocols of CTs, observational studies, and CUPs, while strengthening pharmacovigilance. For instance, Italy has streamlined[32] and centralised the procedures for CTs, observational studies, and CUPs protocols, subjecting them to approval by the scientific committees of the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) and the Ethics Committee of the Lazzaro Spallanzani Institute for Infectious Diseases (Article 40, Law-Decree No. 23/2020, converted into Law No. 40/2020)[33].
Likewise, the French Medicines Agency (*Autorité Nationale de Sécurité du Médicament*, ANSM) has accelerated the assessment of CT authorization applications[34] and CUPs[35], while strengthening pharmacovigilance for anti-Covid-19 off-label uses[36]. No derogations on informed consent procedures are envisaged in France[37]. The Spanish Medicines Agency (*Agencia Española de*

[31] https://ec.europa.eu/growth/content/coronavirus-commission-issues-questions-and-answers-help-increase-production-safe-medical_en (last visited 14/4/2021).
[32] AIFA, *Circolare sulle procedure semplificate per gli studi e i programmi di uso terapeutico compassionevole per l'emergenza da Covid-19*, 22 May 2020.
[33] According to AIFA, the informed consent form is still a mandatory document to be submitted to the Ethics Committee during pandemic CTs. The collection of informed consents could follow alternative paths, like telephone calls, followed by e-mail confirmation or validated electronic systems, but the written template shall be obtained at the very first occasion, see AIFA notice, *Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency*, 7.4.2020 https://www.aifa.gov.it/documents/20142/871583/Comunicato_gestione_studi_clinici_in_emergenza_COVID-19_EN_07.04.2020.pdf/77493ac7-b799-5312-837d-b5f256f63c59 (last visited 14/4/2021)
[34] https://www.ansm.sante.fr/Activites/Essais-cliniques/COVID-19-Essais-cliniques-en-cours/(offset)/0 (last visited 14/4/2021).
[35] *Autorisations Temporaires d'Utilisation*: https://www.ansm.sante.fr/Dossiers/COVID-19/AMM-ATU-essais-cliniques-visas-publicitaires-vos-demarches-durant-la-pandemie/(offset)/7 (last visited 14/4/2021).
[36] ANSM, *Pharmacovigilance et addictovigilance dans le contexte du COVID-19 : une surveillance renforcée*, https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Systemes-de-vigilances-de-l-Agence/COVID-19-Dispositif-renforce-de-Pharmacovigilance-et-d-Addictovigilance/(offset)/0 (last visited 14/4/2021).
[37] Bird & Bird, *Clinical Trials: France. Emergency legislation* https://www.twobirds.com/~/media/pdfs/in-focus/coronavirus/lsh-tracker/clinical-trials_france.pdf?la=en&hash=4C12B58C20B2D1E249B0D87D6CE6D5E53FCA1441 (last visited 5/4/2021).

Medicamentos y Productos Sanitarios, AEMPS) has also streamlined CTs and observational studies[38]. AEMPS provided scientific advice on CTs[39] and recommendations on anti-Covid-19 off-label uses based on CTs and observational studies[40]. AEMPS also facilitated access to potential anti-Covid-19 treatments through CTs or CUPs, while reinforcing pharmacovigilance[41]. Some other Member States have gone even further with NCAs granting national emergency MAs for vaccines not authorised by EMA (e.g., Hungary with the Russian *Sputnik V* and Chinese *Sinopharm* Covid-19 vaccines)[42].

Finally, MDs have been addressed at the national level as well. While Notified Bodies have shared several applicable standards[43], NCAs have issued guidelines for manufacturers. For instance, AIFA clarified how manufacturers can apply for derogations to standard approval procedures[44], and ANSM streamlined the approval of "innovative" MD solutions, e.g., 3D-printed MDs[45].

Generally, neither national emergency legislations and NCAs' recommendations on medicines and MDs seem to include specific information and consent obligations in favour of patients. Among the jurisdictions considered in this paragraph, it is worth noting the remarkable exception of France, where physicians have a specific obligation to disclose to patients the unauthorised regulatory status of a prescription (Arts. L. 5121-12-1, III, *Code de la Santé Publique*). In the case of accelerated MAs, the lack of specific information and consent obligations may result in the under-protection of patients receiving treatments approved with less complete data, *de facto* turning them into subjects for "a continuing trial".

4. Data protection issues

In parallel with informed consent for treatment, the blurring between research and clinical practice monitoring poses several interrelated challenges also to personal data protection. They are related to the research activities connected to the pandemic and might refer either to patients or healthy

[38] AEMPS, *Actuaciones de la AEMPS para agilizar y fomentar los ensayos clínicos y estudios observacionales sobre COVID-19*, MUH, 11/2020.

[39] AEMPS, *Información sobre investigación clínica sobre la COVID19*, 19 November 2020, https://www.aemps.gob.es/laAEMPS/docs/NI_AEMPS-investigacion-clinica.pdf?x98091 (last visited 14/4/2021).

[40] AEMPS, *La AEMPS informa sobre el buen uso de medicamentos relacionados con COVID-19*, MUH, 9/2020.

[41] AEMPS, *Tratamientos disponibles sujetos a condiciones especiales de acceso para el manejo de la infección respiratoria por SARS-CoV-2*, 9 July 2020, https://www.aemps.gob.es/laAEMPS/docs/medicamentos-disponibles-SARS-CoV-2-8-7-2020.pdf?x98091 (last visited 14/4/2021). Informed consent shall be obtained avoiding the risk of contagion, allowing the recording of the patient's willingness orally obtained and preferably before a witness, see AEMPS, *La AEMPS informa sobre el buen uso de medicamentos relacionados con COVID-19*, MUH, 4/2020.

[42] The Czech Republic and Slovakia have also considered authorising the Sputnik V vaccine autonomously (E. HOLT, *Countries split from EU on COVID-19 vaccines*, in *Lancet*, 397(10278), 2021, 958, doi: 10.1016/S0140-6736(21)00620-6).

[43] A.G. FRASER, P. SZYMAŃSKI, E. MACINTYRE, M. LANDRAY, *Regulating drugs, medical devices, and diagnostic tests in the European Union: early lessons from the COVID-19 pandemic?*, cit., 2140-2144.

[44] ITALIAN MINISTRY OF HEALTH, *Richieste di Autorizzazioni in deroga ai sensi dell'art. 11, comma 14 del D.Lgs. n. 46/97 ed Emergenza COVID 19*, 5 May 2020.

[45] ANSM, *Impression 3D pour la fabrication de dispositifs médicaux dans le cadre de la crise du Covid-19*, 2020.

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persons in the process of identifying possible causes and solutions to the covid-19 related diseases[46]. As anticipated, several protocols and projects have been designed to accelerate the detection, diagnosis, and treatment of the disease, as well as to prevent the virus diffusion (mostly restrictions on gathering and movement of individuals). In fact, the need for introducing measures to map the spread of the virus and, at the same time, to adopt effective organizational measures to protect privacy sparked a challenging debate on how to balance the public health and data protection.

Since the very first legislative initiatives on the matter it has been sought a concrete balance between the protection of patients' fundamental rights and the need to accelerate the procedures. Both research for treatment and the control of the spread of the virus have triggered a much-heated debate across the world[47]. At the EU level concerns over personal data processing and the risks to data subjects unfolded in guidelines referring both to research and to contact tracing. In both instances individual and collective right to health (treatment and prevention) have been at the fore for a balancing exercise with other fundamental rights and liberties ranging from the freedom of movement to personal data protection. Key elements on both accounts have been offered by the European Data Protection Board (EDPB).

On April 21st, 2020, the European Data Protection Board adopted the *Guidelines 03/2020 on the processing of data concerning health for the purpose of scientific research in the context of the COVID-19 outbreak*[48], addressing how to comply with the principles stated in the Regulation (EU) No 679/2016 – General Data Protection Regulation (GDPR) in the Covid-19 emergency context.

A driving principle in them is that public health purposes, which require simplified, but effective, procedures, shall not compromise the GDPR principles, so that the value of personal data is preserved while they are re-used for research purposes. A clear guidance is provided by the Recital 46 GDPR, quoting «*humanitarian purposes, including for monitoring epidemics and their spread*» as a possible scenario to pursue «*an interest which is essential for the life of the data subject or that of another natural person*» under «*important grounds of public interest*» giving content to the provision of art. 9.2. *sub* i.

The mentioned EDPB Guidelines identifies the possible sources of health data, including (a) those «*information collected by a health care provider in a patient record*»; (b) those «*that become health data by cross referencing with other data thus revealing the state of health or health risks*» or other information related to a specific context; (c) those provided during "self-check" surveys. It is important to note that this non-exhaustive list envisages the possibility of data integration/fusion from different environments (e.g., medical records, tracing activities, and self-check) acknowledging the possibility and benefits of a data driven approach. Nevertheless, the message is clear: those

[46] EUROPEAN COMMISSION, *Joint European Roadmap towards lifting COVID-19 containment measures*, available at: https://ec.europa.eu/info/sites/info/files/communication_-_a_european_roadmap_to_lifting_coronavirus_containment_measures_0.pdf (last visited 14/4/2021).

[47] See for example, contributions included in VV.AA., *Opinio Juris in Comparatione*, Special Issue 2020, available at: https://www.opiniojurisincomparatione.org/ (last visited 14/04/2021; B. BOUDREAUX *et al.*, *Data privacy during pandemics*, Rand Corporation, 2020; W. NAUDÉ, *Artificial Intelligence Against COVID-19*, IZA, 2021.

[48] EDPB, *Guidelines 03/2020 on the processing of data concerning health for the purpose of scientific research in the context of the COVID-19 outbreak*, 21.4.2020, https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_guidelines_202003_healthdatascientificresearchcovid19_en.pdf (last visited 14/4/2021).

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activities are legitimate and possible under the GDPR's rules without undermining its protective scope. After all, we can add it is its actual scope to lay «*down rules relating to the protection of natural persons with regard to the processing of personal data and rules relating to the free movement of personal data*» (art. 1) at the same time and it is in its DNA to enable a continuous balance of interacting fundamental rights and liberties.

Indeed, building on the very structure of the GDPR, *Guidelines 03/2020* recall the main principles enabling a compliant re-use of personal data and, at the same time, boosting the development of research activities in the context of COVID-19 as well. In particular, the framework identified by article 89 GDPR together with 9.2 *sub* i) and j) GDPR provides the required boundaries to handle sensitive data in the aim of containing the pandemic and for the related research activities[49].

In the scenario of Covid-19, the needed assessments involving the GDPR regulatory system balancing data subjects' rights and data controllers' obligations has unfolded along two main lines and specific aims: (i) to enable systems of tracing, tracking, treating (the so called 3Ts) as the main methodology to combat the virus[50]; and (ii) to ensure that fundamental rights are preserved and protected through the technical and organisational measures in terms of governance of flows and corresponding data retention. It is worth noticing again that the fundamental right to data protection has been sustained (at least by the EDPB) as a driving force to ensure that other fundamental rights and liberties keep their level of protection. In this way, the right to data protection becomes a functional but not subservient fundamental to the protection of individual and collective rights to health; it becomes an essential element to ensure that the right to health can be better deployed (e.g., so that potential infected persons can be warned - saving lives - without exposing them to limitations in access to healthcare services, for example, or to social discrimination).

Similarly, and at the level of research on the other hand, the right to protection of personal data is functional to avoid that the collective interest might, during the pandemic or once the state of emergency has ceased, choose individuals or minorities to be sacrificed directly or indirectly to a majority, altering the difficult balance between the individual right and the collective interest in health. Indeed, a clear example of how personal data have been used to these purposes is the contact tracing App developed in the first months after the world pandemic was declared [51].

Another challenging topic involving Covid-19 containment and data processing concerns the EU health passport and its possible re-use outside airports. While it is clear that the electronic nature of such a vaccination certificate (as what it is, after all) might only raise concerns about its cybersecurity, concerns that could be easily solved with current standard technology, it is also clear

[49] E. VENTRELLA, *Privacy in emergency circumstances: data protection and the COVID-19 pandemic*. *ERA Forum* 21**,** 2020, 379–393, https://doi.org/10.1007/s12027-020-00629-3; M. KĘDZIOR, *The right to data protection and the COVID-19 pandemic: the European approach*. *ERA Forum* 21**,** 2021, 533–543, https://doi.org/10.1007/s12027-020-00644-4

[50] EDPB, *Guidelines 04/2020 on the use of location data and contact tracing tools in the context of the COVID-19 outbreak*, 21.4.2020, https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_guidelines_20200420_contact_tracing_covid_with_annex_en.pdf (last visited 14/4/2021).

[51] G. COMANDÉ, M. MONTI, *App-lichiamo la privacy: considerazioni sulla tutela dei dati personali nello sviluppo delle app di tracciamento*, in M. MALVICINI, T. PORTALURI, A. MARTINENGO, *Le parole della crisi. Le politiche dopo la pandemia. Guida non emergenziale al post-Covid-19*, 2020, Naples, 93 *et seq*.

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that it might entail a different level of risks for fundamental rights and liberties if it is used beyond its envisaged purpose of *facilitating* cross border travelling. Here the risk is reuse or a function creep. In the first case, for instance, if data for the issuance of the EU health passport is re-used beyond their original purpose it could undermine trust in it and the whole voluntariness of adhesion to it. Furthermore, if its original purpose is twisted, and, even if by law, it is requested to grant access to reopening activities (e.g. access to gyms is granted only to EU health passport holders) discrimination concerns and conflicts with other constitutional tenets might arise. An example is offered by the fact that vaccination is not offered to all individuals at the same time because of priority criteria. While it could be useful to facilitate the reopening of certain activities by enabling vaccinated individuals to them, it still be problematic under the right to equality.

Also in this case, the balance between simplified procedures and data protection cannot *be considered as a precondition for free movement, and any measures shall be adopted to avoid possible discrimination against those who do not hold a health passport*[52].

More in general, Authors[53] have already remarked how the Italian emergency legislation described the cases in which it is justified to process personal data under Articles 6, 9, 10 of the GDPR, excluding any derogation from the technical and organizational measures to be adopted for its processing: the Italian emergency statute of March 9th, 2020 deals with personal data processing in its Article 14, providing specific legal conditions for authorized data controllers to enable or disable personal data flows in execution of the emergency plan.

In particular and for example, the Italian provisions identify the subjects that are authorized to carry out the processing of personal data belonging to special categories of data and judicial ones, as long as they are «*necessary for the performance of the functions assigned to it in the context of the emergency caused by the spread of COVID*». Thus, procedural facilitations have a clear and narrow personal scope and purpose that do not undermine the aims of the GDPR while extending the traditional scope of art. 9 GDPR. For instance, medical and health care personnel naturally included under art. 9.2. *sub* i include, according to the mentioned Italian statute, the civil protection staff, public and private structures operating in the health sector, entities appointed to ensure the implementation of emergency measures ensuring that facilitations are applied across the board without discriminations but not beyond what is needed. Other categories of personal data flows (like the general data under Article 6 GDPR) or sensitive and judicial data flows processed with public and private entities other than the above-mentioned categories can be enabled only if «*essential for the performance of activities related to the handling of the health emergency in progress*». With reference to this possible extension, the principles of minimisation, proportionality and purpose limitation identified in article 5 GDPR remain fully applicable.

A modular approach can be appreciated when considering the measures aimed at facilitating data flows within the clinical context: only emergency medical personnel is exempted from providing the

[52] R.C.H. Brown, J. Savulescu, B. Williams, *et al.*, *Passport to freedom? Immunity passports for COVID-19*, in *Journal of Medical Ethics*, 46, 2020, 652-659.

[53] G. Comandé, D. Amram, G. Malgieri, *The democracy of emergency at the time of the coronavirus: the virtues of privacy*, in *Opinio Juris in Comparatione*, [S.l.], mar. 2020, available at: http://www.opiniojurisincomparatione.org/opinio/article/view/144/152 (last visited 14/4/2021).

privacy notice or is authorized to formulate a simplified one, as stated in Article 23, paragraph 1, *sub* e GDPR. In any case, as a minimal guarantee, it is required to communicate at least orally these limitations to the data subjects in order to avoid any risk of information asymmetries or the generation of privileged positions[54]. Therefore, transparency and data minimisation principles remain key to maintaining an accountable approach towards personal data flows during the emergency in the clinical context as well.

In contrast, the principle of accountability, as the mechanism to demonstrate any adopted organizational and technical measure, finds some limitations to avoid any negative impact on the speediness of healthcare procedures. To this end, as far as the internal authorizations delegating the processing within the given organization are concerned, the above-listed categories - as long as they are "front line" operators - can be provided orally authorizing to access the data flows. These exceptions introduce temporarily simplified procedures to allow a proper allocation of resources and time towards healthcare activities, without entirely compromising the GDPR system of duties and rights. Their temporary nature clearly requires that once the emergency declaration is called off the regular procedures need to be reinstated and the appointment will need to be done again in writing with clear and detailed instructions.

A year after the described emergency statutory law, it could be interesting to analyse possible mechanisms of monitoring and assessment of the law in action in order to verify whether or not the stated boundaries are still effective to solve the illustrated balance.

5. The role of informed consent

The described structural mechanism of temporary exceptions introduced in Italy, as an example of a more general issue, within the main boundaries of the GDPR principles find application also in the design of clinical trials. Under Article 17 of the recalled emergency statute, research protocols on Covid-19 shall be submitted to the appointed national competent ethical committee. This measure developed a privileged channel for researchers to access standard procedures to design and implement clinical trials[55].

An important part of a clinical protocol concerns patients' information sheet and informed consent. As known, informed consent to participate in a clinical study shall be distinguished from the legal basis for data processing, as clarified by the EDPB[56]. However, both legal provisions deal with the transparency of the procedures to make the participants / data subjects aware of what could happen and how this could impact their life. Human dignity is preserved if the initial information asymmetry is covered by a transparent information that allows the individuals to understand, to maintain the control on her data / performed activity and to make their decision on participating to the procedure / trial.

[54] *Ibid.*

[55] Art. 40, D.L. 8 aprile 2020, n. 23 on "*Disposizioni urgenti materia di sperimentazione dei medicinali per l'emergenza epidemiologica da COVID*".

[56] EDPB, *Guidelines 05/2020 on consent under Regulation 2016/679*, available at: https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_guidelines_202005_consent_en.pdf (last visited 14/4/2021).

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The informed consent template is composed of three main forms: the information sheet, including all information related to the study (sponsor, funding program, purposes, tasks / activities required and corresponding benefits / risks, contacts to withdraw / ask for information, insurance details, the incidental findings policy etc), the privacy information notice according to articles 13 and 14 GDPR (including the information on data controller, DPO, type of data processed, means, purposes and legal basis, data retention policy, and rights that the data subject may exercise), and the informed consent templates where the research subject may consent to all / any activities of the study. The three documents shall be provided to the participants who is able to freely give their consent without any pressure and fully understanding that no disadvantages are envisaged if they decide not to take part to the trial.

In the context of pandemic research, the Italian ISS Bioethics Working Group provided some remarks[57] considering the peculiar situation of vulnerability of Covid-19 patients. In fact, if the observational studies are not performed in a clinical centre, informed consent can be digitally collected in order to comply with the movement restrictions. In these cases, particular attention shall be paid to the fulfilment of the recruitment conditions and to possible (also transient) incapacity.

One, possibly positive, consequence on consent for both CT and its related personal data processing activities is the acceleration of the already ongoing process of virtualisation for CTs. Indeed, the rush towards forms of *eConsent* (e.g., *Bring Your Own Device -BYOD*[58]) or any other form of progressive virtualization of CTs[59] has been boosted by the need to close existing CTs or to establish quickly new ones.

For Covid-19 patients in clinical centres, the EMA distinguished three scenarios[60]. The first one concerns the oral consent, that is allowed, in presence of witness who can sign in place of the patient, if it is difficult to obtain a written one because of her specific conditions (e.g, isolation). The second one relies with the deferred consent when patient's conditions are critical, and it is possible to collect it at a later time[61]. In this case a written justification shall be provided by the clinicians to justify the choice. The third one recalls the case, where the renewal of consent is required, for example if there are some amendments to the protocol. According to this approach alternative procedure can be implemented to collect the informed consent only if properly justified by the pandemic situation itself. For instance, consent of Covid-19 patients who are incapacitated (e.g.,

[57] ISS, *COVID-19 Bioethics Working Group, Research ethics during the COVID-19 pandemic: observational and, in particular, epidemiological studies*, May 2020, available at: https://www.iss.it/documents/5430402/0/Rapporto+ISS+COVID-19+n.+47+EN.pdf/ef384c21-d41a-65f2-6e66-f7aace63c664?t=1602261818760 (last visited 14/4/2021).

[58] https://www-01.ibm.com/common/ssi/cgi-bin/ssialias?infotype=AN&subtype=CA&htmlfid=897/ENUS220-409&appname=USN.

[59] E.*g. Electronic Patient Reported Outcomes Measures (ePROs) ; Electronic Patient Reported Experiences Measures (ePREMs); Electronic Clinical Outcomes Assessment (eCOA); or Synthetic Control Arm.*

[60] EMA, *Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. version 3*, 28 April 2020, Brussels, 2020.

[61] R. VAN DER GRAAF, MA. HOOGERWERF & M.C. DE VRIES. *The ethics of deferred consent in times of pandemics*. *Nat Med*, 26, 2020, 1328–1330, https://doi.org/10.1038/s41591-020-0999-9.

isolation) may be given orally by the trial participant (as in the case of Article 2 *sub* j of Directive 2001/20/EC) in the presence of an impartial witness[62].

Exemptions are instead envisaged only if stated by the law. This is the case where it is not possible to acquire the data subject's informed consent even from third parties, for data processing «*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*»[63].

Both for personal data processing and informed consent for research purposes, the general ethical legal framework allows for some derogations to promote the fights against the pandemic. These temporary and limited derogations are in any case framed in a solid architecture to protect fundamental rights. A clear example of them is the reach of art. 49.1. *sub* a and d GDPR, enabling «a transfer or a set of transfers of personal data to a third country or an international organisation» allowing for derogations but only on a temporary basis. Thus, the general architecture of the GDPR allows temporary derogations (e.g., to share trial data for vaccines) and not for longer-term post-emergency projects for which the normal rules would apply again.

6. Conclusions and further research

Before the Covid-19 epidemic broke out, the EU pharmaceutical / MD regulation was already experiencing a gradual blurring between medical research and practice, with the movements for early access[64] and 'learning' healthcare systems[65], along with the increasing scientific and regulatory importance of real-world data gathered from clinical practice monitoring[66]. This is challenging the conventional distinctions underpinning the regulatory framework, which has rigidly segregated research and therapy since (at least) the seminal Belmont Report[67]. Mostly focusing on accelerated approval, the regulatory responses to the Covid-19 pandemic have significantly accelerated this trend. A similar trend has interested the virtualization of trials and the process to acquire consent to the trial and to the related data processing. This may theoretically result in experimental uncertainties being transferred to the real-world treatments. This prompted pharmaceutical (and medical device) regulators to compensate for the lack of data comprehensiveness at the time of

[62] See above para 3.4. for the national implementations.

[63] ITALIAN DATA PROTECTION AUTHORITY, *Coronavirus and data protection*, available at: https://www.garanteprivacy.it/temi/coronavirus/faq (last visited 14/4/2021).

[64] S. PATIL, *Early access programs: Benefits, challenges, and key considerations for successful implementation*, in *Perspectives in Clinical Research*, 7(1), 2016, 4-8, doi:10.4103/2229-3485.173779.

[65] A. BUDRIONIS, J.G. BELLIKA, *The Learning Healthcare System: Where are we now? A systematic review*, in *Journal of Biomedical Informatics*, 64, 2016, 87-92, doi: 10.1016/j.jbi.2016.09.018.

[66] A. CAVE, X. KURZ, P. ARLETT, *Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe*, in *Clin. Pharmacol. Ther.*, 106, 2019, 36-39, doi: 10.1002/cpt.1426.

[67] N.E. KASS *et al.*, *The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight,* in *The Hastings Center Report*, 43(1), 2013, S4-S15, doi: 10.1002/hast.133; F.G. MILLER, *Revisiting the Belmont Report: The ethical significance of the distinction between clinical research and medical care*, in *Newsletter on Medicine and Philosophy*, 5(2), 2006, 10–14. The Belmont Report itself was, however, aware of the limitations of such a rigid divide. This is made clear by its recommendations concerning 'innovative' clinical practice, for which some kind of oversight was advised (https://www.hhs.gov/ohrp/regulations-and-policy/belmontreport/index.html, last access 14/4/2021).

approval with the strengthening of post-marketing monitoring, where observational research plays an increasing role. Although these processes need to be welcomed, we argued that these trends have deep implications for the data protection and for an effective informed consent of patients. Indeed, both data protection and informed consent regulation offer ways to reconcile simplified procedures and protection of patients' fundamental rights.

Once acknowledged that the pandemic has only accelerated processes already set in motions by the expansive use of big data in medical and epidemiological research and by the need to virtualize several moments of CTs it appears clear the need to further investigate how to reap all the benefits of the evolutions we mentioned without diluting the safeguards envisaged by the regulation and the general principles to protect human dignity and patients' autonomy without impairing the accelerating pace of scientific research.

From the above analysis emerged how the unfolding of flexible approaches, relaxing pragmatically some rules but accompanying them with safeguards (e.g., temporary nature of derogation, reinforcement of protective measures by way of PASs and PAESs, safeguards against function creeps) in the context of the pandemic is the track on which CTs and their interplay with personal data protection law will unfold in the close future. This magmatic and fast evolving scenario certainly deserves further research and a more comparative analysis for which we should not wait the end of the world pandemic.

Special issue

Ethical and legal requirements for biomedical research involving health data in the context of the Covid-19 pandemic: is informed consent still playing the leading role?

Federico de Montalvo Jääskeläinen*

ABSTRACT: The current pandemic could have accelerated a change of the traditional paradigm about the secondary use of health data. The traditional one has been based on the faculty of the individuals about accepting or not that use of their health data through the main role of informed consent. The new paradigm considers the current value of that secondary use for the improvement of the health of community and its individuals, through the possibilities offered by Big Data and AI. Therefore, the need of a balance between individual rights and the common good is indispensable. Pseudonymization could be the way to find this balance.

KEYWORDS: Data protection; health data; informed consent; privacy; pseudonymization

SUMMARY: 1. Big Data and the opportunities of secondary use of health data for improvement of medicine and health – 2. Is my health data mine anymore? – 3. Is there a clear legal solution at the EU regulatory framework? – 4. Has informed consent a main role in this new context of secondary use of health data? – 5. Conclusion.

1. Big Data and the opportunities of secondary use of health data for improvement of medicine and health

Big Data offer new opportunities for the development of our societies and for solving many of our current economic and social problems in general, but most specifically in the field of health research. The extensive use of conventional health data and even their interlinking with non-traditional data shall help to fight against many diseases and to develop new treatments which is a new hope for patients and for all the community. The results extracted from data use took decades to obtain only a few years ago. Currently, because Big Data and AI, it can be revealed within months, even days, and, above all, at a very affordable cost. Algorithms enable the comparison of a large number of healthcare processes, thus offering accurate conclusions, in terms of volume, on the most acute diagnosis and the best treatment for many diseases.

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The context is, therefore, unique from an historical perspective and not taking advantage of it could be seem as a not very ethical option, above all, if we consider the opportunities offered for the prediction, prevention or healing of many diseases. Furthermore, this unprecedented scenario unfolds at a time when new uncertainties grow about the evolution of several diseases, which although very well known, such as cancer, offer new paradigms of cell and protein development, as well as of new diseases, many of which are untreatable yet (i.e. orphan diseases). The interactions among the determinants of countless diseases are highly complex. Big Data enable researchers to integrate and aggregate information from across multiple sources. The opportunity is therefore undeniable from the perspective of the protection of life: this requires that we discard an *a priori* approach that conceives health-related data processing negatively.

As the German Ethics Council (*Deutscher Ethikrat*) pointed out, in biomedical research, the analysis of large volumes of health data should provide a better understanding of important scientific processes and their connections. Among the most data-intensive applications are modern imaging and molecular biological procedures, such as those employed in what we call 'omics' (e.g. genomics or proteomics[1]).

Also, this idea is explicitly recognized in the EU Regulation 2016/679, April 27, 2016, on the protection of individuals with regard to the processing of personal data and on the free movement of such data (hereinafter referred to as the EU Regulation). In fact, Recital 157 of the Regulation explicitly notes, "By coupling information from registries, researchers can obtain new knowledge of great value with regard to widespread medical conditions such as cardiovascular disease, cancer and depression. On the basis of registries, research results can be enhanced, as they draw on a larger population. Within social science, research on the basis of registries enables researchers to obtain essential knowledge about the long-term correlation of a number of social conditions such as unemployment and education with other life conditions. Research results obtained through registries provide solid, high-quality knowledge which can provide the basis for the formulation and implementation of knowledge-based policy, improve the quality of life for a number of people and improve the efficiency of social services. In order to facilitate scientific research, personal data can be processed for scientific research purposes, subject to appropriate conditions and safeguards set out in Union or Member State law".

Thanks to the massive use of data, results analysed collectively have a different value than results analysed individually. As Professor Vanesa Morente highlighted very clearly, the use of Big Data brings a deeper, and more significant insight, that goes beyond the obvious. Professor Morente uses a paradigmatic metaphor to explains the phenomenon: it is like an onlooker who may spot a human face in Giuseppe Arcimboldo's still lives only contemplating them as a whole, when the painting is a mere conglomerate of separate and assorted fruits and vegetables. The primary purpose of Big Data entails therefore a look that not only sees, but also discovers: it is a transformative look that sees value in raw, unprocessed information[2]. In the medical and health contexts in general, this has an

[1] GERMAN ETHICS COUNCIL, *Big Data and health. Data sovereignty as the shaping informational freedom*, Opinion, Executive Summary and Recommendations, Berlin, 2018, p. 9.

[2] V. MORENTE PARRA, *Big data o el arte de analizar datos masivos. Una reflexión crítica desde los derechos fundamentales*, in *Revista Derechos y Libertades,* 41 (época II), 2019, p. 2.

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unquestioned value, because unlike other research fields, this sector attaches a particularly relevant value to the quantitative method, even though, as they say, there are no illnesses, but rather patients. In any case, in order to improve medical treatments further, the opportunity to correlate millions of healthcare processes is fundamental, in that these results shall later be contextualized and personalised.

This opportunity has even more value and projection for the future in those States, such many of the EU Member States, which have implemented a public healthcare system where there is a correlation among millions of medical records and health data.

In the view of the definition given by the World Health Organization a few years ago, whereby health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity", a holistic approach to health should blur the line between health seen from the medical perspective and lifestyle. Big Data provide the technical opportunity to support such a holistic vision, as they do not confine data use to strictly or traditionally health-related data, such as clinical records, but also integrate data on a person's lifestyle, habits and even environment.

On the other hand, these new opportunities of the development of new technologies, Big Data or AI pose some ethical and legal conflicts and dilemmas. Health data is one with a strict regulation and legal protection considering the impact of their revelation in individuals' privacy.

There are risks to personal rights, as there are opportunities. This is why the German Ethics Council specified that Big Data represent a major challenge to the legal system and, in particular, to constitutional law. Nonetheless, personal information goes hand in hand with these risks, even more so in areas such as healthcare, where highly sensitive data are at stake. However, Big Data will potentially multiply these risks[3]. In fact, they are not only limited to the right to privacy, since information on a person's health status can affect other rights and interests, such as access to employment, credit or insurance[4].

In any case, the balance between the individual rights and the common good or general interest is, sometimes, not very easy to fulfil. In any case, principle of proportionality always offers an ethical and legal pathway to do so, above all, from the perspective of the subprinciple of proportionality *stricto sensu* or balancing[5].

2. Is my health data mine anymore?

This question could be seen as a strong one or, at least, a tricky one. In any case, as we explained before, new technologies and mainly Big Data offers a great number of new opportunities in the area

[3] GERMAN ETHICS COUNCIL, *Big Data and health. Data sovereignty as the shaping informational freedom*, Opinion, Executive Summary and Recommendations, Berlin, 2018, p. 10.

[4] R. MARTÍNEZ, *Big data, investigación en salud y protección de datos personales ¿Un falso debate?,* in Revista Valenciana d'Estudis Autonòmics, 62, 2017, p. 236.

[5] The point of the balancing stage is to determine which of the two (or more) values at stake takes priority in the concrete circumstances of the case. In other words, the question is whether the interference with the right is justified in light of the gain in the protection for the competing right or interest. To this end, the two values have to be "balanced" against each other. Vid. K. MÖLLER, *Proportionality: challenging the critics*, in *I.Con*., 10 (3), 2012, p. 715.

of health where we have a huge amount of data coming from medical records, clinical trials protocols, internet consultations, etc.

Consequently, it can be stated that clinical data are no longer a mere reminder of the healthcare process, but rather the main source of knowledge and progress in Medicine and Biology. Health data can already be considered as the true treasure of biomedical research, as many said that biological samples were the treasure of the previous decade.

In any case, considering risks and conflicts for individual rights, health data and biological samples are not the same, above all, if we consider the possibilities of anonymization or pseudoanynomization of data which are not identical for samples. Protection of individual identity from whom biological sample comes is not an easy task, because samples carry the genetic identity of the individual. But when we are talking about data, the possibilities of protecting his or her identity is not an unsolvable problem anymore.

In the healthcare field or in a specific clinical trial, data are not strictly of interest as documentary evidence of the most relevant facts concerning the treatment provided, treatment-related decisions or the diagnoses and conclusions reached, but for their secondary use. It is independent from the main purposes for which those data were initially provided. Patients contribute their data for a specific purpose and such data can be useful for a secondary purpose, or use, enabled by the tools offered by Big Data.

Moreover, the opportunities offered by the extensive use of health data become even more relevant in healthcare systems characterized by both essentially public management and care provision schemes (the Beveridge formula) and the recent process of digitalization of documents and clinical records, that helped introduce millions of data in a single or, at least, in easily comparable databases. Consequently, we are not exclusively referring to data extracted from research projects on humans or clinical trials, but to the secondary use of health data, which is more significant in terms of numbers and, possibly, value.

From an ethical perspective, as the Spanish Bioethics Committee said on its Report on the ethical-legal requirements in research with health data and biological samples in the framework of the Covid-19 pandemic, 2020[6], maintaining the postulate that the disease and the data generated by its treatment only belong to those who suffer it is not only to ignore reality, but also to ignore the existence of conflicting values and rights and the correct way in which they should be reconciled. Data protection is not, nor has it ever been, an end in itself, but rather serves to protect the person in their privacy, both in their private sphere and in the public sphere. However, it is also important to remember that this right to privacy, like other rights, plays in a social environment of interrelations, in which it is as relevant to recognize the autonomy of the individual as the solidarity of the citizen.

A similar position is supported by Barbara J Evans: those who invoke their right not to share their data in any circumstance, even when the health of third parties may depend on them, may be blurring the line between individual autonomy and narcissism[7]. A position that ignores the common

[6] http://assets.comitedebioetica.es/files/documentacion/Informe%20CBE%20investigacion%20COVID-19.pdf. (last visited 31/05/2021)

[7] B.J. EVANS, *Big Data and individual responsibility*, in GLENN COHEN et al (ed.), *Big Data, Health Law and Bioethics*, Cambridge University Press, Cambridge, 2018, p. 21.

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good and prioritizes not only autonomy but even selfishness and narcissism does not seem acceptable from an ethical-legal perspective. Also, for Ricard Martínez, there is a change of paradigm towards a new one based on efficient control by the authorities of the use of data from an initial consent[8].

In this regard, UNESCO's International Declaration on Human Genetic Data says in its Art. 14 that human genetic data, human proteomic data and biological samples associated with an identifiable person should not be disclosed or available to third parties, such as employers, insurance companies or relatives of the person in question, except for an important reason of public interest. And when we are talking about the value of secondary use of health data for the health of others, the public interest could be seen as a clear one.

The International Bioethics Committee, IBC-UNESCO, pointed out in its 2017 Report on Big Data in health, that Big Data can already be considered a common good of humanity (literally, "Big Data can be framed as a common good of humankind"). Science and technology in the field of Big Data can help reduce the inequalities that prevent many human beings from enjoying the highest possible level of health, both nationally and internationally. Therefore, it can be said that health data, in the Big Data stage, is a true heritage of humanity, even if it is in merely metaphorical terms. However, the provision of this Big Data cannot be carried out at the cost of violating the right that each individual has.

3. Is there a clear legal solution at the EU regulatory framework?

Despite the above-mentioned relevance of Big Data in general and in healthcare in particular, the European legal framework has not issued any specific regulation. It is true that there is a very complete regulation on personal data protection by the European Union and several parts of this regulation may apply to Big Data. However this is a new reality that may require more specific solutions. Therefore, the problem is not a dearth of general regulations, since several legal conflicts and dilemmas are legally covered by the data protection regulation, but rather of specific provisions and perhaps new principles apt to govern the innovative characteristics of Big Data.

In any case, the new EU regulation, while not specifically addressing the particular dilemmas and conflicts of Big Data, does contain specific references to health data and, more specifically, to the requirements for their secondary use for research purposes. We may say that the Regulation opens up a new era or even a new paradigm in this field. In fact, it replaces the model based on the alternative between informed consent and anonymization, with one based on informed consent or pseudonymization that would enable a more flexible use of health data in the interest of the community and everyone's good health.

From an ethical-legal standpoint, we do not believe that we can apply the ethical-legal principles and values developed for Big Data-driven research to traditional research projects on humans, because the rights involved in research projects not focused on individuals, but on their data differ. It is no longer a matter of affecting an individual's integrity, but rather intruding in his or her private sphere.

[8] R. MARTÍNEZ, *El alcance e interactuación del régimen jurídico de los datos personales y big data relacionado con salud y la investigación biomédica*, in Rev Der Gen H, 52, 2020, p. 59.

Furthermore, one might ask whether a regulatory model, based essentially on an individual's interest, still responds to citizens' desires. In this respect, some works have already shown that citizens do not oppose data sharing; on the contrary, as Haug stated, patients want their data to be shared quickly, especially to ensure that other patients may learn of any possible treatment-related adverse events. At the same time, they also want to retain some control on how the data are shared, particularly when the research purposes are essentially commercial and not so much when public health systems seek to use data to improve medical treatment or care for other patients. In fact, receiving medical care invariably involves a loss of privacy. Patients must disclose their personal information to obtain help, and that help generally derives from knowledge gained from the experiences of previous patients who disclosed their personal information. The problem is not so much in the use, but in the demand for responsible use[9].

Obviously, this cannot mean prioritizing collective interest at the expense of individual interest, but rather seeking a balanced formula to integrate the two. This formula can be worked out when we safeguard the rights of the individuals involved by adapting one of the two requirements that the new legal model of data protection seeks to accomplish, i.e. anonymization through the new mechanism of pseudonymisation.

What is relevant in this new model is not so much an individual's prior consent to the new purpose for which data are intended or strict data anonymization. In fact, what matters is the legitimate origin of the data, the great importance of their secondary use for community health and the adoption of sufficient measures to prevent non-authorised third parties from gaining access to an individual's identity through the data, without necessarily demanding any strict anonymization. This seems to be legally achievable through what is commonly named pseudonymisation, defined by the EU Regulation as the processing of personal data in such a way that they can no longer be attributed to a specific individual without the use of additional information, as long as that such additional information is kept separately and subject to technical and organisational measures of non-attribution to an identified or identifiable individual.

The advantages of pseudonymization over traditional, strict anonymization are clear from the standpoint of community health. In fact, interlinking the data to the person, even when it is extraordinarily difficult for a third party to decode them, means not only to broaden the data used in a research to include other initially insignificant data (data enhancement), but also to corroborate the results of data use with the patients' real progress (results verification), for example. And this is very relevant in today's Big Data science. Pseudonymisation is, in the end, the only guarantee against the previously mentioned misleading causalities that are one of the main risks of Big Data.

In short, against this backdrop of great opportunities in the fight against disease and in the improvement of people's health, it is important to promote new paradigms that do not present technology only as something essentially good that totally excludes human intuition and wisdom. In fact, such models should not neglect that the context has deeply evolved over the years and the enormous advantages of massive data processing must go beyond a vision exclusively based on

[9] C.J. HAUG, *Whose Data Are They Anyway? Can a Patient Perspective Advance the Data-Sharing Debate*?, in NEJM, 26th April 2016, pp. 1-2.

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individual interest at the expense of the common good. As it is in many other areas, true virtue seems to assert itself as the centre of gravity between the two approaches.
Furthermore, the debate must be addressed so as not to lose sight of the context. In the health protection models developed in Western Europe after the Second World War and, above all, in those based on a social-democratic formula such as the Beveridge model, it would be contradictory to maintain a position only taking into account the individual or the subjective dimension, in that those models feature essential traits of communitarianism. Going to a hospital and having a serious health problem solved thanks to public spending demands that citizens exercise their responsibility that is manifested, in the current context of technological progress, in the moral duty to share their data so that others who have not been so easily and readily treated can benefit from medical care.

4. Has informed consent a main role in this new context of secondary use of health data?

If the secondary use of health data offers the opportunity to know what is the best chance of overcoming the disease for those who are suffering from it or who may unfortunately suffer from it in the future, can we sustain a presumed paradigm of the absolute sovereignty of the individual about her or his personal data? It seems that Big Data has not only substantially altered the form and method of research in Medicine, but also the nature of conflicting rights and interests. And all this makes more sense if possible, in a context such as the current one, of a pandemic as serious as the one we are suffering.
The general interest never justifies the sacrifice of individual rights. If there are situations in which Bioethics must inform decision-making in an unavoidable way, they are precisely those in which all our values are put in tension, and when the error of giving priority almost exclusively to the collective interest in detriment to the dignity and rights of the individual. Bioethics was born in the context of a crisis and it is precisely in moments of greatest difficulty that it reveals its fundamental role, providing the framework for reflection and deliberation that allows the most appropriate ethical decisions to be taken. Seeking the right balance between the common good and the rights of the individual must be the main target.
Thus, in the new framework offered by the advancement of science and technology through the secondary use of health data, when projects are of obvious common or general interest, the requirement of a new informed consent for a different use of data can be not attended for three fundamental reasons, following again the opinion of the Spanish Bioethics Committee (Report on the ethical-legal requirements in research with health data and biological samples in the framework of the Covid-19 pandemic, 2020)[10]:
Firstly, because obtaining a new consent to the secondary use of the data means allocating a large part of the personal and material resources of the projects to a different purpose than that of health research itself. Furthermore, obtaining such authorization in the current context can be very difficult, if not impossible when we are talking about a huge amount of data as Big Data usually implies. Certainly, this reason is relevant, but it may not be considered sufficient.

[10] http://assets.comitedebioetica.es/files/documentacion/Informe%20CBE%20investigacion%20COVID-19.pdf. (last visited 31/05/2021)

Therefore, the second and most important reason that informs in favour of dispensing with the requirement of a new consent to carry out research with a great interest for public health or for the protection of the health of third parties, has to do with the scope of the right from the individual to his privacy within the framework of the society in which he develops his life. If certain conditions do not meet in a society, people's rights are nothing more than empty expressions. The Universal Declaration of Human Rights recognizes this when it states that "everyone has the right to establish a social and international order in which the rights and freedoms proclaimed in this Declaration are fully effective" (art. 28).

A third reason, closely related to the previous one, to justify not requiring a new specific informed consent in certain investigations, has to do with the duty of solidarity that we all have as members of a community. That duty is the condition of possibility of individual realization. Once again, the Universal Declaration of Human Rights summarizes it: "Every person has duties with respect to the community, since only in it can he freely and fully develop his personality" (art. 29.1).

When the preservation of a good of enormous importance for all, such as public health, requires carrying out research with personal data collected in the context of health care, its use may be justified without the need to request specific consent, provided that the guarantees for the safeguarding of the essential content of the right to privacy concur. The traditional paradigm of informed consent poses important problems from an ethical perspective.

As Barbara J Evans points out again, our legal model for medical and biomedical research has been based on the main role of informed consent as a guarantee of the privacy of the individual. However, this model responds to a different reality from the one now offered to us because current research, unlike that which gave rise to the great bioethical documents linked to research such as the Nuremberg Code or the Declaration of Helsinki, does not aims to act on the integrity of people, but on their data. It does not touch the person but their data. We are not facing physical integrity of the individual and collective interest, which would hardly pass the proportionality test, and, above all, the limit of dignity as the essential core of the right, but privacy. It is a new informational research that, neither ethically nor legally, can be equated with clinical trials that can put the integrity of the subject at risk. In Big Data environments, traditional individual informed consent standards can no longer fulfill the primary purpose for which they were designed[11]. And in a similar way, the Institute of Medicine of United States distinguishes between interventional research and research that is exclusively information based[12].

Therefore, we are talking about a different paradigm to the one traditionally called Helsinki paradigm. The so-called Helsinki paradigm refers to the bioethical and legal postulates promoted after the events that occurred in the field of research with human beings at the end of the first half of the 20th century and even a few years later. Bioethics and Biolaw were inaugurated as specific areas of knowledge on the occasion of the those execrable attacks on the dignity and human rights (see Willowbrook State School, Jewish Chronic Disease Hospital Of New York, or Tuskegge Syphilis Study, as sadly paradigmatic examples). Bioethical and bio-legal reflection arise as walls of

[11] B.J. EVANS, Op. Cit., pp. 26-27.

[12] Institute of Medicine, *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health through Research*, The National Academies Press, Washington DC, 2009, p. 3.

containment or prevention against the abuses that can be committed in the field of research, expressing with the counterphrase erroneously attributed to Machiavelli, or, at least, with the pejorative meaning with which it habitually is used, that the ends do not justify the means or the collective interest the sacrifice of the dignity of the individual.

Both Bioethics and Biolaw were born as areas of knowledge with a foundational purpose: the development of guarantees for human dignity in the field of research with human beings. And these guarantees were included in the Nuremberg Code and later in the Declaration of Helsinki, approved by the World Medical Association in 1964. In both the new model inaugurated is based on the strict protection of individual interest, as a reaction to the abuses that occurred a few years before.

And this, precisely, is one of the problems we address. Informed consent, born essentially as a guarantee against atrocities committed at the end of the first half of the 20th century, has ended up postulating the principle of autonomy as the prevailing one, ignoring the context in which it is intended to operate. The problems that the doctrine of informed consent has presented in its evolution are substantially motivated because it arises under the protection of medical research with human beings, intending to implant with the same extension and effects in other areas such as healthcare medicine or of research with data. Although an extraordinarily rigorous compliance with the informed consent makes full sense in a relationship between researcher and subject in which the former is going to act on the life or physical integrity of the latter and in which the individual has to adopt a decision such as participating or not in a clinical trial, whose individual benefit is uncertain. In the research with data, such demands do not seem so necessary.

Furthermore, one might wonder if this legal model, based essentially on the interest of the individual, also responds to the wishes of citizens. In this regard, there are already works that show that citizens do not hold a position against sharing data. As Haug points out, patients want their data to be shared quickly, especially to ensure that other patients are aware of potential treatment side effects. And although it is true that they also want to maintain some control over how they are shared, this occurs especially when the aims pursued by the studies are essentially commercial and not so much when it is the public health systems themselves that intend to use them to improve medical treatment or care for other patients. Patients usually accept to expose their personal information for help, and that help is generally based on knowledge gained from the experiences of previous patients who have disclosed personal information. The problem is not so much in the use, but in the demand for responsible use[13].

The current model where the informed consent should play a main role for research with health data seems more based on the opinion of legislators and the doctrine of some academics than on the true will of the citizens.

Therefore, we can affirm that what is relevant in this new model will not be that the individual has given their prior consent for the new purpose to which the data is intended to be used, but a) the legitimate origin of data, b) the relevance for the general interest of the secondary use, c) and the implementation of enough guarantees to protect the individual's identity from whose data come from. And it seems that, legally, it can be achieved through what is now called pseudonymization, understood, in the words of the EU Regulation, as the processing of personal data in such a way that

[13] C.J. HAUG, Op. Cit., p. 1.

they can no longer be attributed to an interested party without using information additional information, provided that such additional information appears separately and is subject to technical and organizational measures designed to ensure that personal data is not attributed to an identified or identifiable natural person.

The virtues offered by pseudonymization compared to the traditional strict anonymization are evident from the perspective of the interest of the health of the community, since, by maintaining the link between the data and the person, when it is extraordinarily difficult for a third party to decode it, it is allowed not only to expand the data used in the research to others that initially could not be considered transcendent (data expansion) but, which is very important in the current state of Big Data science, to contrast the results of the exploitation of data with, for example, the true evolution of the patients (verification of results)[14]. Pseudonymization is, in the end, the only guarantee against the spurious causalities which is one of the main risks of Big Data at its current stage of evolution.

This is the position of the International Bioethics Committee, IBC-UNESCO, which in the Report on Big Data and Health, 2017, stated (par. 59): "In case research is intended that falls outside the range of the broad consent that was obtained for the use of this data, specific consent is necessary for secondary data processing. This is an essential principle to guarantee confidentiality and data privacy. However, secondary analysis of data could be ethically admissible without a new informed consent for such secondary use provided that all the following requirements are met: 1) appropriate legal foundation; 2) evaluation by the Research Ethics Committee (REC); 3) adequate technical procedures in order to prevent researchers and third parties from accessing personal data, such as pseudo-anonymisation; 4) overriding public interest in this health research; 5) infeasible to obtain a new consent; and 6) data must have been collected according to ethical and legal requirements".

And also the Council of Europe in its Recommendation on Protection of health-related data, CM/Rec(2019)2 (par. 15.9): "Where scientific research purposes allow, data should be anonymised; where research purposes do not allow this, pseudonymisation of the data – with intervention of a trusted third party at the separation stage of the identification – is among the measures that should be implemented to safeguard the rights and fundamental freedoms of the data subject. These measures must be carried out where the purposes of the scientific research can be fulfilled by further processing which does not permit or no longer permits the identification of data subjects".

5. Conclusion

In this new framework of great opportunities to fight against diseases and improve people's health, it is important to promote new paradigms which do not forget that there is a very different context from the existing one a few years ago. The great advantages offered by massive data processing should determine a vision not only based on individual interest with a clear detriment of the

[14] Using the words of The Nuffield Council: "to feed back information to an individual within a cohort who is discovered to be at particular risk, or to validate an analytical procedure, or to enable further data about individuals to be added over time". Vid. NUFFIELD COUNCIL ON BIOETHICS, *The collection, linking and use of data in biomedical research and health care: ethical issues*, The Nuffield Council Publication, London, 2015, p. 68.

common good. A balance between both positions seems to show itself, as it happens in many other areas, as true virtue.

Furthermore, the debate must be framed in terms where the context is also considered. In the models of healthcare developed in Western Europe after the Second World War and, above all, in those based on the more social democratic formula such as Beveridge model, it is a contradiction to maintain a position that only addresses the individual dimension, when the model has essential features of communitarianism.

Between the two main options offered for a real development of the opportunities of secondary use of health data, a new form of informed consent such as dynamic one, taking advantage of the proper technology to give it for new uses of data, or pseudonymization as a flexibilization of strict anonymization, we consider that the second one should prevail for the reasons explained before.

In any case, this new paradigm also needs the development of a real governance of health data to support correctly it. So, accepting a new model based on pseudonymization means to put all our efforts in that target, a new model of co-governance where all the benefits from the massive exploitation of millions of health data should redound to the benefit not of the industry nor the specific individuals from which these data come from, but to all the community.

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