Presidenza del Consiglio dei Ministri

BIOMEDICAL RESEARCH FOR NOVEL THERAPEUTIC TREATMENTS WITHIN THE COVID-19 PANDEMIC: ETHICAL ISSUES

22 October 2020

Presentation

The Italian Committee for Bioethics (ICB) intervenes on the topic of research in the context of the Covid-19 pandemic, focusing attention on the ongoing biomedical research for novel therapeutic treatments, of particular importance in a phase of the pandemic situation in which the search for a vaccine continues, analyzing some of the most relevant ethical issues involved. The pandemic context and the consequent health emergency can constitute a challenge to respect the consolidated requirements of biomedical research for therapeutic purposes, shared by the international community, given the urgency of obtaining results.

In the opinion, the Committee reiterates that, even in the context of the pandemic emergency, the general scientific, ethical and legal criteria of clinical trials are to be respected, as well as the criterion of justice in the allocation of resources at different levels (prevention, diagnosis and treatment of Covid-19 patients without neglecting research on other pathologies) and the standards of quality and validity. The Committee identifies the possibility of accelerating research by strengthening translational research from the laboratory to the patient's bedside, with adequate information provided to the patient regarding the potential risks.

In particular, the ICB focuses on the *off-label* use of drugs and compassionate care, underlining the need for clear communication on the risks to patients and the importance that every effort should be made to proceed according to ordinary experimental designs. Furthermore, the Committee believes that the research aimed at obtaining therapeutic treatments for Covid-19 must include all individuals, without any exclusion (while maintaining an adequate risk/benefit ratio as a prerequisite), considering the exclusion of particularly vulnerable persons from the research as contrary to the principle of justice, as it deprives them of the same possibility of treatment today, as no safe and effective treatment is currently available, but also in the future for the possible exposure to risks. The relevance and role of ethical review by the ethics committees is also underlined, with particular reference to the Italian experience involving the Italian Medicines Agency (AIFA), in particular with the Technical-Scientific Commission, and the Single National Ethics Committee for COVID-19 trials.

The Committee also analyzes the transformations of informed consent for participation in trials in the emergency context of the pandemic, focusing on research on biological samples, genomic tests and the use of data. The Committee's hope is that, on various levels, it is essential to ensure, in the context of the pandemic, interdisciplinary research, collaboration, international coordination and the sharing of results and data for health as a "common global good".

The opinion has made drawn on several topics covered by Profs.: Carlo Caltagirone, Cinzia Caporale, Bruno Dallapiccola, Lorenzo d'Avack, Silvio Garattini and Laura Palazzani, who worked on drafting the text.

The Director General for Prevention at the Ministry of Health, Prof Giovanni Rezza, was audited at the plenary session on June 26, 2020.

The opinion was approved unanimously by those present, with the votes of Profs.: Salvatore Amato, Luisella Battaglia, Carlo Caltagirone, Stefano Canestrari, Cinzia Caporale, Carlo Casonato, Francesco D'Agostino, Antonio Da Re, Lorenzo d'Avack, Mario De Curtis, Riccardo Di Segni, Gianpaolo Donzelli, Silvio Garattini, Mariapia Garavaglia, Marianna Gensabella, Laura Palazzani,

Tamar Pitch, Lucio Romano, Massimo Sargiacomo, Luca Savarino, Monica Toraldo di Francia and Grazia Zuffa.

Despite their not having the right to vote assent was given by: Dr. Maurizio Benato, the delegate for the President of the National Federation of MDs and Dentists Colleges; Dr. Carla Bernasconi, the delegate for the President of the National Federation of the Orders of Italian Veterinarians; Dr. Amedeo Cesta, the delegate for the President of the National Research Council; Prof. Carlo Petrini, the delegate for the President of the National Institute of Health.

Prof. Paola Di Giulio, the delegate for the President of the Superior Health Council, absent at the time of voting, subsequently assented.

The following members not present at the session subsequently expressed their support, Profs: Bruno Dallapiccola, Maurizio Mori, Assuntina Morresi, Lucetta Scaraffia (present at the plenary session, but absent at the time of the vote).

The Covid-19 pandemic has provided and provides a strong impetus for biomedical research and, specifically, in the experimentation of novel treatments, in order to quickly find safe and effective treatments. To date, numerous therapeutic trials have been launched some of those underway show encouraging results[1].

The pandemic context and the consequent health emergency can constitute a challenge to respect the consolidated scientific, ethical and legal requirements of biomedical research for therapeutic purposes, shared by the international community. The scientific and social uncertainty raised by the pandemic and the strong and urgent need for treatment could induce researchers, physicians and the participants themselves to improperly accelerate research, however the urgency to achieve results must not compromise compliance with these requirements.

The Committee therefore draws attention to the following aspects of ethical and social importance.

1. The Committee reiterates that, even in the context of the pandemic emergency, the general ethical criteria of clinical trials are to be respected, also defined in terms of legal regulation: the scientific justification of the validity of the trials, the balancing of risks/benefits and the protection of the health, safety and well-being of the patient, informed consent related to treatments and the use of biological samples, protection of privacy and data protection, the scientific-ethical review of independent ethics committees, and verification of the absence of conflict of interests for all personnel involved in the studies[2].

2. The Committee reiterates the importance of the criterion of justice in the allocation of resources at different levels. Research in the context of Covid-19 requires proportionate intervention in the prevention, diagnosis and treatment of affected patients, without however neglecting research on other pathologies and the use of funds for the treatment of all patients[3].

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[1] Ongoing Covid-19 research studies: 1,972 studies worldwide, of which 72% for therapeutic purposes, 16% for preventive purposes, 5% for supportive therapies; 64 studies in Italy, of which 92% for therapeutic purposes and 8% for preventive purposes.

[2] The international regulatory framework on experimentation begins with the *Nuremberg Code* (1947), through the *Declaration of Helsinki* (1964 and subsequent revisions) and the elaboration of clinical practice guidelines (Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* adopted in 1993 with subsequent revisions*; Good Clinical Practice* approved by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use in 2002), up to documents with international and community relevance, binding to varying degrees. In particular, the following should be mentioned: Unesco, *Universal Declaration on Bioethics and Human Rights*, 2005; Council of Europe, *Convention on Human Rights and Biomedicine*, 1997 and *Additional Protocol concerning Biomedical Research*, 2004; *the European Union Regulation* no. 536/2014 of April 16, 2014 on clinical trials of medicinal products for human use, which repeals Directive 2001/20/EC.

[3] It should also be noted that the pandemic is adversely affecting the conduct of clinical trials initiated (in some cases) prior to the current health emergency. In an editorial, the Journal of the American Medical Association (JAMA) drew attention to the importance of continuing clinical trials during the pandemic (including the adopting of alternative data collection strategies) and called on investigators to consider the results objectively, explicitly acknowledging the uncertainties about the results deriving from the pandemic (T. R. FLEMING, D. LABRIOLA, J. WITTES, *Conducting Clinical Research During the COVID-19 Pandemic Protecting Scientific Integrity,* in "JAMA", 2020 May 28).

3. The pandemic emergency can push for an acceleration of trials for therapeutic purposes[4] which, in any case, must comply with the scientific standards of quality and validity: trials must not be started without a technical-scientific evaluation. It should therefore be reiterated that the pandemic context does not justify in any case research that is not scientifically supported[5].

4. The Committee believes that the need to accelerate trials, without prejudice to the necessary compliance with ethical principles, must give rise to an increase and strengthening of translational research (*from bench to bedside*). Since it takes too long to translate the results of preclinical research (from the *bench* of the laboratory) into clinical applications (to the patient's *bedside*), the goal of translational research is to make the advancements in research knowledge immediately usable for a biomedical impact on health by implementing therapeutic tools. However, since this context may involve greater risks for patients, it will have to be the subject of comprehensible and specific information provided to the patient. The acceleration involves consolidation of the bond between biomedical research and clinical practice. The hope is that, in the context of Covid-19, there will be even closer interaction between these areas. In this regard, the role of Research bodies, Universities, Scientific Institutes for Research, Hospitalisation and Healthcare (IRCCS) and the National Institute of Health which operate with a view to integrating experimental clinical research with clinical practice, seems fundamental.

5. In the context of the Covid-19 emergency, given the rapid spread of SARS-CoV-2, the serious clinical condition of some patients, the absence of resolutive care and the urgency of treatments for the protection of personal and social health, there is a strong drive towards the *off-label* use of drugs[6], for clinical conditions that differ from those for which their marketing has been authorized (as per Law 648/1996), or towards the "compassionate" use of drugs, still in the experimental phase, which are used, on the basis of a defined clinical protocol or on a nominal basis for a single patient, outside the clinical trials already in progress, in patients for whom it is believed that there may be a clinical benefit but who are without the possibility or the necessary requisites to be included in those research studies[7] (in Italy this is regulated by the Ministerial Decree

[4] World Health Organization (WHO), *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks*, 2016; Nuffield Council on Bioethics, *Research in Global Health Emergencies: Ethical Issues*, 2020. See also http://www.enrio.eu/enrio-statement-research-integrity-even-more-important-for-research-during-a-pandemic/.

[5] To this end, the Italian Medicines Agency (AIFA) Technical Scientific Committee (CTS) was appointed in Italy to review all the research studies of Covid-19 therapies. The advisory opinion of the CTS is implemented by the Single National Ethics Committee for Covid-19, which, in turn, evaluates the study and issues a single national opinion. Art.40 of Decree Law 8 April 2020 no.23 attributes this role to the Ethics Committee of the National Institute for Infectious Diseases "Lazzaro Spallanzani" - IRCCS.

[6] The Italian Medicines Agency has taken steps to facilitate the early access to therapies for the treatment of COVID-19 disease, authorizing the use of some *off-label* drugs (included in the list provided for by Law 648/1996).

[7] Compassionate use or therapeutic use has been widely applied in the Covid-19 emergency, in all the countries of the world, both on individual patients, with nominative authorization, and through compassionate use programs on thousands of patients, based on standard criteria identified in advance. The Committee has addressed the issue in an earlier opinion, *Single patient care and non-validated-treatments (the so-called "compassionate use"*). *Accompanied by a juridical note,* 27 February 2015, recalling the ambiguity of the expression "compassionate" and deeming more correct the expression "non-validated treatments for personal and non-repetitive use", as it captures elements common to the different types described. The Committee reiterates the importance of rigorous observance of the trial phases recognized by the international

07.09.2017). In both situations, adequate and specific information regarding the risks to the patient must always be provided.

The Committee believes in particular that access to therapies not yet validated through compassionate use should not constitute hidden or fictitious experimentation, which intends to obtain results by improperly shortening the times of the usual trial procedures to test the safety and efficacy of treatments. In this regard, while considering the drama of the Covid-19 epidemic, which partly justifies a wider use of compassionate drugs, the Committee believes that every effort must be made to proceed according to normal trial designs.

Furthermore, the Committee believes that in general the trial times can and should be reduced by simplifying the administrative procedures for the approval of research, without circumventing the scientific, ethical and legal requirements of clinical trials.

6. Trials aimed at therapeutic treatments for Covid-19 must include all subjects - according to the most appropriate phases and timing - without excluding anyone, unless there is an unfavorable risk/benefit ratio[8]. The exclusion of particularly vulnerable subjects from the trial is contrary to the principle of justice, as it deprives them of the same possibility of treatment, as no safe and effective treatment is currently available[9].

Furthermore, this exclusion would also have consequences in a future perspective, if there were drugs recognized as safe and effective, as those who do not participate in a trial are exposed to higher risks, since the balance between risks and benefits is not verified for their specific condition[10]. The trial should be modulated according to the specificity of the participants or groups of participants[11].

7. Informed consent remains a fundamental requirement for participation in the trial. In the context of the pandemic emergency, it presents some peculiarities compared to standard methodologies.

It is essential that researchers realistically balance the potential benefits and risks for research participants: a) avoiding excessively risky trials, in the face of possible limited benefits; b) communicating risks in a clear and transparent way to the potential participants; c) adapting them to the specific conditions of the patients, including situations of particular vulnerability, and to the specific phase of the research[12]. Information from the researcher must also be transparent in the clarification of uncertainties: it is necessary to verify the participant's understanding, preventing, in the context of the pandemic, the perception of the risks from being decreased, in the face of expectations that are not always

community and recalls that access to compassionate treatment must be subordinated to a reasonable, robust and solid scientific basis (with data published in international journals, and possibly results of Phase I clinical trials, i. e. safety and harmlessness).

[8] See WHO, *Ethical Standards for Research during Public Health Emergencies: Distilling Existing Guidance to Support COVID-19 R&D*: “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 unfavourable benefit-risk ratio”.

[9] To date, there is only one single approved drug for the treatment of Covid-19 on the market.

[10] Particularly vulnerable groups, in the context of therapy trials for Covid-19, refer to individuals with other pathologies, elderly people, pregnant women with the potential to have risks to their own health and the health of the fetus, immigrants who belong to different cultures with different ethnic backgrounds and with difficulties in communication and understanding, children.

[11] Italian Committee for Bioethics (ICB), *Pharmacological trials on women*, 28 November 2008.

[12] Ethical Committees Coordination Centre, *Linee di indirizzo per la raccolta del consenso informato alla partecipazione a sperimentazioni cliniche,* (20 July 2020).

reasonable[13]. Researchers must consider the particular condition of vulnerability in the pandemic context and always evaluate the best interest of the patient, despite possible requests by patients to participate in the Covid-19 trial for therapeutic purposes. Furthermore, the researcher must give consideration to informed consent in relation to the development of the disease over time (as there are many decisions to be taken at different times), gauging the right moment for the patient, considering the ability to understand and the emotional state of the patient (e. g. fear, anxiety etc.).

In a clinical emergency situation, in compliance with the health protocols in relation to SARS-CoV-2, exceptions to traditional written consent are allowed through the use of digital consent or oral consent in the presence of witnesses. In the latter modality, it is important to provide patient guarantees by means of third parties, that is, an impartial witness external to the health care team - and possibly even to the facility - or also, where possible, with relatives on video call. When the patient is not in a position to receive and understand the information, but is affected by pathological conditions for which there is no alternative treatment and it is not possible to promptly consult the trustee or a legal representative, any consent or authorization to prolong participation in the trial, with potential direct benefits, must be requested when and under the conditions in which it is reasonably possible to do so[14]. The doctor must comply as far as possible with the indications of any "advance treatment directives" or "shared care planning" (Law 219/2017), and the indication of a trustee.

In the case of changes to research protocols, which are frequent due to the evolution of the pandemic, consent must, as far as possible, be requested including the appropriate amendments.

8. During the Covid-19 pandemic, numerous biological samples are taken, also in the context of diagnoses and epidemiological investigations, using swabs and/or blood samples, as well as in the context of trials for therapeutic purposes.

The Committee stresses that informed consent must always be required for the acquisition of biological samples, even in the case of serological tests and swabs[15], specifying whether they are collected for diagnostic and/or research purposes. In analogy with the ordinary practice of clinical research, the consent must specify the time, place, methods of conservation of the samples and the purposes of the research, specifying whether it is directly related to the research on Covid-19, as well as any subsequent use of samples for compatible purposes.

The Committee believes that, given the urgency and importance of biomedical research for humanity in the context of the pandemic, it is important to encourage for clinical research purposes the use of biological or clinical

[13] Where it is not possible to obtain informed consent in the usual manner, due to movement restrictions or patient isolation or urgency, alternative procedures must be considered. Methods of consent obtained also using video recording provided for in Law 219/2017 must be taken into account.

[14] As according to the *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research* (2005), art. 19 c. 3: “Consent or authorization for continued participation shall be requested as soon as reasonably possible”; *Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials of medicinal products for human use and repealing Directive 2001/20/EC,* art. 35, c. 2 the “informed consent to continue participation in the clinical trial is acquired by the subject as soon as he/she is able to provide informed consent”. See also ICB, *Clinical trials in adult or minor patients who are unable to give informed consent in emergency situations*, 28 September 2012.

[15] See Tuscan Regional Bioethical Commission, Opinion no. 6, 12/06/2020, *Infezione da SARS CoV2 - Test sierologici e molecolari: informazione e consenso.*

material residual from previous diagnostic or therapeutic activities, defining homogeneous criteria for the use of biological samples, taking into account the procedures for accessing and acquiring the patient's consent on the subsequent use of the sample taken[16].

In this sense, the ICB hopes that the consent relating to biological samples in the context of the Covid-19 pandemic will be broad, i.e. open to future uses of the samples for research. In any case, the security of conservation and the protection of privacy with pseudonymisation must be guaranteed[17] in the manner that must be specified in the consent, in order to avoid any abuse and to be able to trace the identity of the subject in case of results of clinical relevance[18]. In the case of biological samples taken from minors, the consent must be issued by the parents and, upon reaching the age of majority, a new consent must be requested from the subject for their conservation and use, unless they are anonymised[19].

The Committee expresses the hope that the Covid-19 pandemic will serve as an opportunity to inform society on the meaning and importance of clinical research on biological samples[20]. The ICB calls for biological samples to be donated to research.

9. Aware that this phase of transition from basic knowledge to clinical applications is characterized by great uncertainty and dynamism, as knowledge about the virus is likely to be quickly surpassed, the Committee believes that genomic investigations and diagnostic tests on patients are of substantial aid to research and its clinical applications, particularly as regards understanding the basics of the individual response to SARS-CoV-2 infection. In this context, it is important to inform the patient about the possibility of unexpected results (incidental findings[21]), allowing, through coding, to trace the identity of the subject for any relevant information on a clinical and/or existential level, with the foresight of the protection, as far as possible, of privacy, and provided that the patient has previously given consent to receive information of this type (specifying if he/she wants to be informed about unexpected results and what kind of results, if any, to know). In this context, genetic counseling is of particular importance.

10. The collection of personal data in the context of participation in research must be accurate, according to the criteria of quality, accessibility, transparency, standardization, interoperability and sharing. Data are a valuable asset, as they contribute to the advancement of knowledge, and also offer a potential direct

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[16] The guidelines provided for in Article 1, paragraph 1, letter b, Legislative Decree 14 May 2019 n. 52 in preparation by the National Institute of Health.

[17] Pseudonymisation, using several techniques, allows protection of the sensitive personal data of an individual, in order to make them not directly attributable.

[18] See previous opinions of the ICB on the topic: *Biobanks and research on human biological material*. *Opinion of the NBC on a Recommendation of the Council of Europe and on a document of the National Committee for Biosecurity and Biotechnology,* 9 June 2006; *Collection of biological samples for research: informed consent,* 16 February 2009 (mixed group with the Italian Committee for Biosafety, Biotechnology and Sciences of Life - CNBBSV)*; Pediatric biobanks*, 11 April 2014.

[19] ICB, *Pediatric Biobanks*, 11 April 2014.

[20] In the event of a refusal, the samples can be anonymised (i. e. in a manner that can no longer be traced in any way to the person from whom they were taken by eliminating all 'personal' information), and kept for other research or destroyed once the purpose for which had been collected in an emergency has been achieved. The samples must also be anonymised in the event of the patient's death, in the absence of his/her explicit consent to collection and storage in biobanks for Covid-19.

[21] ICB, *Managing "Incidental Findings" in genomic investigations with new technology platforms*, 17 March 2016.

benefit to the patient, as well as an indirect benefit to society[22]. It is essential to monitor the correct storage of data in reliable and certified deposits, with the guarantees of compliance with ethical requirements and legal rules, preventing abuse[23]. An explicit consent must be provided – where possible – related to using or not using the data for compatible future research.

11. It is imperative, in the context of the pandemic, to ensure international collaboration and coordination on the level of public research, as highlighted by numerous international documents[24]. Competition between research in the private sector must also be geared to improving knowledge with a view to widening the access to results. Research on an international scale must be given priority along with the dissemination of research findings[25] for the common global good. Given the urgency of treatments, it is desirable for researchers to share research results and share patient data (*data sharing*) at every level, also in order to avoid duplication or undersized research.

12. In general, in the various countries, the ethics committees evaluating the trials must be able to adapt to the needs of the emergency, facilitating and easing ethical review in a short time, given the urgency and without derogating from fundamental ethical principles, carefully monitoring the safety and protection of the rights of participants, especially those who are most vulnerable[26]. In Italy, the speed and accuracy of the process is ensured by the emergency procedures provided by the government which involve AIFA, in particular the Technical-Scientific Commission, and the Single National Ethics Committee for Covid-19 trials. This model, which is being tested for the Covid-19 pandemic, allows for the acceleration of study approvals, while maintaining scientific requirements. This model could also be applied to other areas.

13. The Committee underlines the importance, highlighted by the Covid-19 pandemic, of promoting and incentivizing interdisciplinary research, increasingly important for the purpose of solving problems of a collective interest and therefore of strong ethical value, through the enhancement of such research in the procedures for the recruitment of researchers, in the definition of public calls for research funding in all sectors, as well as in the evaluation of research products.

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[22] 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*, 26 March 2020. In particular, Research Data Alliance (RDA), *Recommendations and Guidelines*, 28 May 2020 which refers to the FAIR principles for the collection of data, namely Findable, Accessible, Interoperable, Reusable and underlines the need for *sharing data*; WHO, *Information Sharing on Covid-19*, 29 March 2020.

[23] The rules are established in *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) and in the exceptions to data protection in Italy (Legislative Decree no.101 of 10 August 2018). See the National Institute of Heatlh (ISS) document, *Data protection in Covid-19 emergency,* Bioethics COVID-19 Working Group, no. 42, 2020.

[24] WHO, *Statement, Developing Global Norms for Sharing Data and Results during Public Health Emergencies* (September 2015); Organisation for Economic Co-operation and Development (OECD), *Why Open Science is Critical to Combatting Covid-19,* 12 May 2020; *Fair Findable, Accessible, Interoperable and Reusable. Principles of Data Sharing in Public Health Emergencies*, June 2018.

[25] European Group on Ethics in Science and New Technologies*, Statement on European Solidarity and the Protection of Fundamental Rights in the COVID-19 Pandemic*, 2 April 2020.

[26] *Position of the European Network of Research Ethics Committees (EUREC) on the Responsibility of Research Ethics Committees during the COVID-19 Pandemic*, 27 April 2020.