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

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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.

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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).

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

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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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