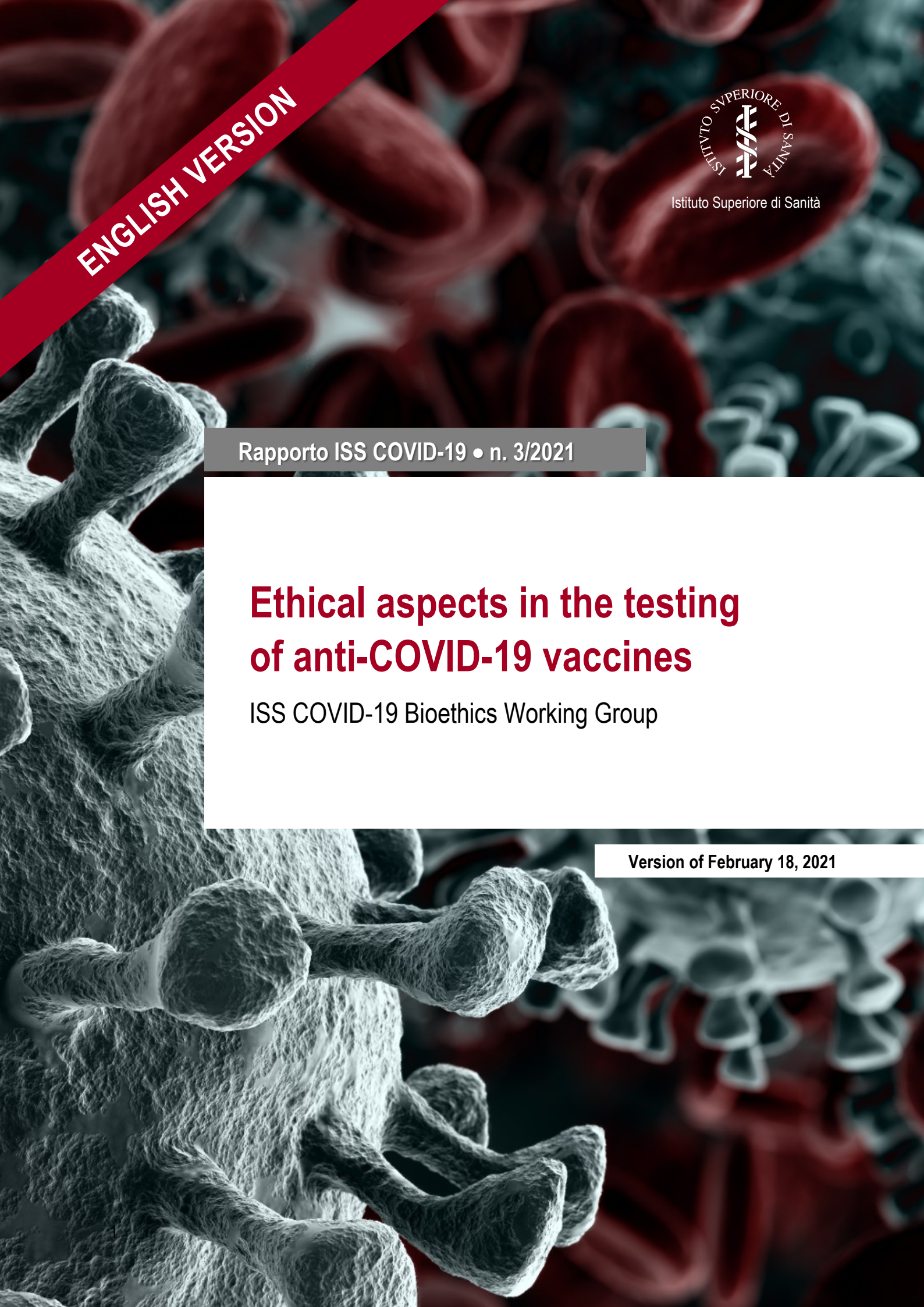

ENGLISH VERSION

Istituto Superiore di Sanità

Rapporto ISS COVID-19 • n. 3/2021

Ethical aspects in the testing of anti-COVID-19 vaccines

ISS COVID-19 Bioethics Working Group

Version of February 18, 2021

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Istituto Superiore di Sanità
Ethical aspects in the testing of anti-COVID-19 vaccines. Version of February 18, 2021.
ISS Bioethics COVID-19 Working Group
2021, iv, 38 p. Rapporti ISS COVID-19 n. 3/2021 English version

The pandemic caused by the new SARS-CoV-2 virus is driving the need to test and approve new vaccines quickly. The report enucleates the ethical criteria that must be respected in this context. It describes the scientific and methodological aspects underlying the experimentation of vaccines, the regulatory aspects, the procedures adopted to reduce the time needed to grant authorizations. It highlights the need to not deviate from the rigor of the methodology and the ethical requirements that must always be guaranteed, even in emergency conditions.

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Special thanks for the intense and painstaking work are due to: Dr Sabina Gainotti, for the drafting of the text; Dr Cristina Morciano and Dr Elena Toschi, of the Research Coordination and Support Division (ISS), for their precious suggestions; Dr Carlo D'Aprile, for the editorial form and graphic design.

Cite this document as follows:

ISS Bioethics COVID-19 Working Group. *Ethical aspects in the testing of anti-COVID-19 vaccines Version of February 18, 2021.* Roma: Istituto Superiore di Sanità; 2021. (Rapporto ISS COVID-19 n. 3/2021 - English version).

The responsibility for scientific and technical data lies with the authors, who declare that they do not have any conflict of interest.

Editing and graphics: ISS Scientific Communication Unit (Sandra Salinetti and Paola De Castro)

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Preface

In a letter dated May 14, 1796, Edward Jenner refers to the vaccination experiments that he began in 1749. In the course of the second half of the century, in a sequence of experiments he injected serum from the pustules from human smallpox and serum from cowpox into various people, including his eight-year-old son Edward Jr., other children, and some servants. Edward Jr. showed signs of mental retardation, he was a sickly child and died at the age of 21. In 1798 Jenner published "An Inquiry into the Causes and the Effects of the Variolae vaccinae, a disease known by the name of Cow Pox". Jenner's theory was at first scorned, but only two years later it was widely accepted.*

However, no one made any comments regarding the involvement of vulnerable people. Jenner's experiments ushered in the age of vaccines and marked an epoch-making turning point in the history of medicine. Today Jenner's experiments would be totally out of the question. Should we, then, regret the times when the absence of rules allowed freedom for any medical procedure? Has ethics imposed a straitjacket on scientific research? Certainly not: ethical criteria and scientific rigor are most necessary. Experimentation with human beings, in fact, may violate human rights and values: two centuries after Jenner, Jean Bernard, President of the French Comité Consultatif National d'Éthique pour les Sciences de la Vie et de la Santé, wrote that "Research involving individuals is morally necessary and necessarily immoral".

Researchers and doctors who are steadfastly sure of their science are as ridiculous as Doctor Purgon who, in "The Malade Imaginaire", is described by Molière as "a thorough doctor from head to foot, a man who believes in his rules more than in all the demonstrations of mathematics, and who would think it a crime to question them. He sees nothing obscure in medicine, nothing doubtful, nothing difficult".

The COVID-19 pandemic has made the need for effective vaccines, as well as treatments, most urgent. The topic of vaccines is very broad and challenging and it includes research, production, distribution, and placing vaccines within a comprehensive plan that addresses public health.

In this report, the "Bioethics COVID-19" Working Group of the Istituto Superiore di Sanità (ISS, the Italian National Institute of Health) does not address the entire panorama of ethical issues concerning vaccines (which would include research, production, distribution, allocation, and planning of public health), but focuses only on the ethical aspects relating specifically to clinical trials.

Under the pressure of the pandemic, procedures have been adopted for the trials on COVID-19 vaccines that were unthinkable only a short time ago (e.g., speeding up the regulatory procedures) as well as completely exceptional practices in the field of human experimentation (e.g., "challenge trials", in which healthy volunteers are deliberately infected with the virus). These innovations will leave a mark on how trials are carried out even once the emergency will be over. The positions presented and discussed in this Report,

* 'Variolisation' however was not invented by Edward Jenner: it had been practiced for centuries. In the 16th century it was widely used in China. In 1661 it was decisive in the history of the Qing dynasty. Smallpox was present among the Manchu population and caused the death of the Emperor Fu-lin. His son K'ang Hsi contracted smallpox during his childhood and survived. For this reason, he was the favourite child in the household since his brothers had not contracted the disease and were therefore more vulnerable. For this reason, K'ang Hsi became Emperor. Once he came to power, he organized a variolisation campaign among his troops and had his own child to variolised. Variolisation was practised for centuries in different parts of the world, especially in Turkey. Lady Mary Worley Montague, wife of the British Ambassador to the Country promoted the practice in England. Her engagement induced the Royal Family to be variolised and carry out the so-called "Newgate experiment" which involved six prisoners from Newgate. Between 1721, year of the "Newgate experiment" and 1738, English doctors subjected 1738 people to variolisation.

therefore, have a value, especially from an ethical point of view, which goes beyond the pandemic currently underway, and are not limited to reflecting on the vaccines currently under study or recently validated.

The Working Group includes experts, both internal and external to the ISS, who cover multiple disciplinary areas, beyond bioethics: public health, epidemiology, clinical medicine, law, bio-law, nursing sciences, philosophy, paediatrics, palliative care, and others. Thanks to the multiplicity of skills and competences its members have, the "COVID-19 Bioethics" Working Group has produced documents on various ethical issues raised by the pandemic.

To deepen the ethical aspects concerning the clinical trials on COVID-19 vaccines, the Working Group received inputs from the experts of the various departments of the ISS such as the National Centre for Research and Preclinical and Clinical Evaluation of Drugs, the Department of Infectious Diseases, the Research Coordination and Support Service.

The hope is that the report will be of help to those who plan, evaluate, run or participate in trials on COVID-19 vaccines.

However, it is written in plain language, with the aim and hope of offering citizens an accessible text that provides insight into the issue.

Carlo Petrini
Coordinator of the COVID-19 Bioethics Working Group
Director of the Bioethics Unit and President of the Ethics Committee
Istituto Superiore di Sanità

Introduction

In the context of the COVID-19 pandemic, the increasingly predominant focus placed on the development of vaccines is driven by the widely shared opinion, among the scientific world, that vaccines are a necessary and crucial tool in the containment of the virus in the shortest possible time, with all the health, economic, and social benefits associated with a virus free world. This awareness has understandably generated pressure, on a global level, to speed up research and the testing of vaccines, posing urgent and important scientific and ethical challenges.

The basic criteria of the ethics of clinical trials involve in particular scientific value and validity, balancing risks versus benefits, respect for persons, the primacy of the wellbeing of the individual over the interests of the advancement of knowledge, informed consent, fair selection of participants, and independent review.

In addition to the issues that characterize every trial, the testing of vaccines presents additional problems deriving, for example, from the preventive, and not strictly therapeutic, purpose of the product under study.

The COVID-19 pandemic, in turn, presents additional peculiarities compared to other situations, deriving in particular from the expectation, across the world, for an effective vaccine to be available as soon as possible: in the era of "Vaccine hesitancy" there are now high expectations in COVID-19 vaccines, and the review of regulatory procedures for COVID-19 vaccine candidates occurs under intense clinical, economic, and political pressure.

The urgent need for vaccines has also led to envisaging practices that would usually be excluded, such as the "challenge trials", in which groups of healthy volunteers are deliberately infected. Protocols have also been set up in which participants receive payment.

The large number of trials being conducted are quite heterogeneous and vary considerably, not only in terms of stage of advancement, but also because they are based on different approaches, some of which are innovative with respect to the vaccines developed thus far. However, they all have two main objectives in common: reduce the likelihood of becoming seriously ill, and prevent infection by stopping the transmission of the disease.

Even though, in order to provide an adequate scientific framework, mention is also made of pre-clinical trials and management issues, allocation, and organization of public health, this Report focuses specifically on clinical trials, and not on what precedes and follows them*. However, the issue is unavoidably intertwined with queries that go well beyond the experimental work and have to do, for instance, with patents, information, and many others.

The ethical framework proposed in this Report is included in the definition of the scientific requirements: rigor in the scientific method is, indeed, the first requirement of an ethical approach.

From a broader ethical perspective, the topic deserves special attention because it calls into question some characteristic features of current biomedical research: in the era of precision medicine, in which the aim is to develop drugs that are tailored as much as possible to the characteristics of the single individual, research is now seeking to develop treatments that are as universal as possible. After a few decades in which the emphasis was placed on individual autonomy as the cornerstone of clinical ethics, the pandemic has made people and communities more sensitive to population dynamics and to collective, as well as individual, interests. In his analysis of the situation determined by the pandemic, Craig Klugman (Klugman,

* The possible use of cell lines from human foetuses deriving from voluntary pregnancy terminations, with its methodological and ethical implications, is not dealt with in this report.

2020) points out that bioethics has gone too far in the direction of the individual and needs to be redirected towards the importance of community and the common good, and Ruth Chadwick (Chadwick, 2020) calls for solidarity as an important value in bioethics.

This report is being published as the first vaccines are becoming available after having been tested in the months immediately following the appearance of the pandemic. This, however, does not make the report untimely: many trials on COVID-19 vaccines are under way and new ones will be launched, with the aim of not only making various types of vaccines available, but also of addressing the new variants that appear and spread over time. The availability of the first vaccines underlines the need for reflection on the ethics of the testing of COVID-19 vaccines that are nearing completion, those that are still in progress, and those that are under way or will be undertaken in the future in similar circumstances.

1. Trials of COVID-19 vaccine candidates

Key points

- Mass vaccinations have the aim of protecting the population from infectious diseases and of saving human lives. Vaccines must be safe and effective because they are administered to non-infected and often healthy individuals.
- The devastating effects of the COVID-19 pandemic have led to pressing demands for developing in the shortest time effective vaccines capable of protecting as many people as possible; at the same time, a part of public opinion fears that, in the name of pursuing results as swiftly as possible, the scientific rigor of the trials could be overlooked.
- The response to the pressing request for vaccines to be made available on a large scale has resulted in a reduction in the time required for testing COVID-19 vaccines. The application of safety protection strategies has made it possible to overcome most of the limits of acceleration providing scientific evidence on safety.

1.1. Vaccine trials

Even though many months have elapsed since the identification of the SARS-CoV-2 virus, specific therapies for the treatment of the disease caused by this virus (COVID-19) are not yet available. In addition, the rate of spread of the disease and the fact that the pandemic has not ended, as instead happened for the recent epidemic of the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS), have induced the scientific community and industry to believe that vaccines are potentially the most effective measure for fighting against COVID-19.

Vaccines, like any other drug, are developed in accordance with the phases of pre-clinical and clinical experimentation. Before being considered for human use, each medicinal product must undergo a series of tests to evaluate its activity and toxicity both *in vitro* and *in vivo* in animal models.

All the studies carried out *in vitro*, *in vivo* in animals and *ex vivo* are defined as “non-clinical” studies and they accompany the clinical development of medicines, including vaccines.

Of these, the “pre-clinical” studies are conducted prior to the Phase 1 *First In Human* (FIH) clinical trial.

Upon completion, the pre-clinical phase is followed by the clinical development in human, which includes 3 phases:

- **Phase 1.** First administration of the vaccine to human beings to evaluate tolerance and safety of the product (this phase involves a small number of individuals).
- **Phase 2.** If Phase 1 presents satisfactory results, the vaccine is administered to a larger number of individuals (in the order of hundreds) to evaluate the immune response produced, tolerance, safety, and to define the doses and most adequate administration protocols.
- **Phase 3.** If Phase 2 produces satisfactory results, the vaccine is administered to a large number of people (in the order of thousands) in order to evaluate the real preventive function of the vaccine, and hence its efficacy. These are controlled trials (the individuals treated with the vaccine under study are usually compared against individuals receiving placebo) and they are randomized (individuals are randomly assigned to one of the treatment arms). This type of trial is the best method for demonstrating the efficacy and safety of a medicinal product, including vaccines.

If all the phases have a favourable outcome, the vaccine is authorized by the competent health authorities and is hence registered: only at this point it is produced and distributed on a large scale.

- **Phase 4** studies (post-authorization) are conducted after marketing and are aimed at verifying the effectiveness and safety of the vaccine in its real conditions of use, at evaluating its use in particular population subgroups and for given pathological conditions, to verify the benefit / risk ratio with respect to the disease.

Unlike most clinical trials on drugs, vaccine trials are not designed to evaluate a treatment for sick people, but to evaluate the product's preventive efficacy against an infection and / or disease in healthy people.

Therefore, the primary endpoint of a vaccine trial, particularly for Phase 3 studies, is the number of new cases, or the incidence of the infection or disease caused by an agent against which the vaccine was manufactured both in the treatment and control arms of the trial.

The other key endpoint of Phase 3 trials is the incidence of side effects attributable to the vaccine: while minor effects (fever, pain at the injection site, redness) occur in the short term, have an expected incidence of a few dozen percentages (e.g., 20-30%) and are those that most affect the people who receive the vaccine, more serious side effects have a very low incidence and can be detected only if the number of participants is very large and the observation time very long.

Most Phase 3 vaccination trials carried out in the last fifty years required the enrolment of tens of thousands of participants and a duration of several years.

The outcome of a vaccine or drug trial requires a predetermined time of observation (usually years) to permit the detection of an appropriate number of events both in the treatment and in the placebo arms of the trial. The statistically significant difference of the number of events in the trial arms (e.g., vaccine versus placebo) is considered indicative of the treatment efficacy.

However, not all the participants in the trial start treatment on the same day nor do they all complete the trial at the end of the follow-up: each participant contributes for a certain period of time and the enrolment may last months, during which some participants may drop out prematurely, others may even die; therefore, not all participants are followed for a period of time of equal duration.

To calculate the incidence of the event, as denominator is used the **person-time**, i.e., the sum of the time spent in the trial by each person.

The duration of Phase 3 trials on drugs is largely dependent on the number of patients who can be enrolled (longer for rare and shorter for frequent diseases), but the frequency of the endpoint event is usually relatively high and therefore the sample size and observation time after the enrolment are relatively limited.

On the contrary, in vaccine trials, a high number of volunteers can rapidly be enrolled, but the endpoint (incidence of the disease in the arm of the vaccinated individuals *vs*. the arm of individuals treated with placebo), occurs over a much longer period of time. In fact, the majority of infectious diseases for which vaccines are developed have an incidence of few cases per one hundred thousand people per year.

The low incidence makes it less likely for a participant (who received the vaccine or the placebo) to be infected and therefore that an event may occur. This means that a much longer observation time is required.

1.2. Characteristics of COVID-19 vaccines

In the case of COVID-19, the time and procedures required to carry out a conventional vaccine trial clash against the urgent need for mass immunization programmes: mortality from COVID is very high worldwide,

and the distancing measures put in place to stem the diffusion of the virus have catastrophic effects on the economy and on social relations.

The world of research, industry, national and international authorities, economy have all mobilized to respond to the cry of pain coming from society and have taken measures aimed at reducing the time to complete the clinical trials without undermining their quality: million-euro pre-emption contracts for the purchase of vaccines that do not yet exist have been entered into, huge public and private funding has been activated for vaccine research, emergency procedures have been approved by the regulatory authorities to significantly reduce the approval times of vaccines (Ball, 2021). On the other hand, very powerful technologies are currently available for the development of new vaccines, to the point that numerous vaccine constructs were ready as early as March 2020.

To support the development of effective COVID-19 vaccines, pre-clinical and clinical trials have been set up using both traditional and innovative technologies with the aim of identifying the most effective and safe formulations fast to produce on a large scale.

Traditionally, in the production of vaccines the causative microorganism is inactivated, so that it cannot replicate, attenuated so that it does not cause the disease, or genetically modified (recombinant protein subunit).

The strategies that in the past worked for viruses belonging to the same family (SARS-CoV and MERS-CoV) and those against the Ebola and Zika Viruses (ZIKV), have made possible to speed up the development of COVID-19 candidate vaccines by providing important information on immunogenicity aspects for protection and characteristics of safety of the vaccine (Diamond, 2020).

Some COVID-19 vaccines, instead, have been made using nucleic acid sequences that encode specific SARS-CoV-2 molecules. In some cases, the genetic sequence of the virus is conveyed by using liposomes (mRNA placed in tiny lipid vesicles) or by replacing the genetic sequence of another inactivated virus using genetic engineering tools (e.g., DNA in the case of adenovirus, RNA in the case of the measles). Once inoculated into humans, these vehicles allow the genetic sequence encoding specific SARS-CoV-2 molecules to enter into the cells where they are used for the synthesis of the protein against which a specific antibody and cell-specific response is to be induced (Callaway, 2020a).

mRNA vaccines lack the theoretical risk of being integrated into the recipient genome that has been hypothesized for DNA vaccines. Indeed, the mRNA enters directly into the cytoplasm of the cells through microparticles used as vehicles, such as liposomes where it is used in the rough endoplasmic reticulum to synthesize the protein that it encodes, in this case the SARS-CoV-2 Spike protein, and it is subsequently broken down.

In short, this is a “digital” vaccine that does not inject antigens, but only the information required to build them.

A technique already in use in human biology, but new in vaccinology: the brilliant success of this technique opens up a new page in the construction of vaccines and other therapies that could quickly rewrite the entire logic underlying the production of vaccines.

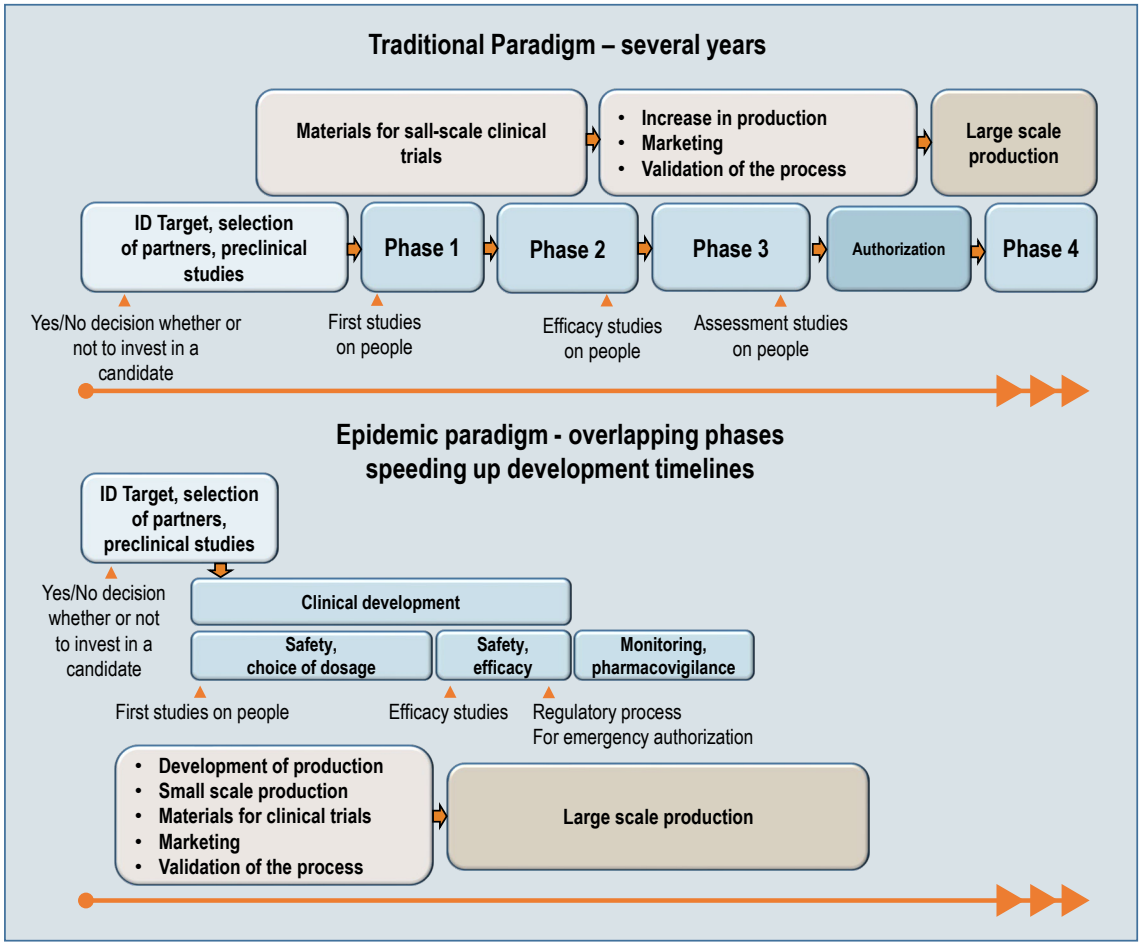
Therefore, the application of highly specialized biotechnologies and the knowledge of vaccine platforms that have already been used have had a special impact on the development of the vaccine against SARS-CoV-2 given the urgent need to provide answers that until a few years ago could be obtained only through the “canonical” timing associated with the development of a vaccine.

In conclusion, both traditional and new approaches based on different technological platforms are being used for the development of COVID-19 vaccines, as following:

- viral vectors, such as human or non-human primate-derived adenoviruses, modified to not cause any disease but encoding the SARS-CoV-2 spike protein;
- recombinant viral proteins (subunits) such as the SARS-CoV-2 spike protein or some of its domains with different adjuvants;
- peptides (portions of SARS-CoV-2 spike protein);
- mRNA or DNA encoding the SARS-CoV-2 spike protein conveyed by virus-like particles (VLP), liposomes or gene-guns;
- VLP;
- inactivated SARS-CoV-2;
- live attenuated SARS-CoV-2.

After completion of Phases 1 and 2 of the clinical trials, large efficacy studies started on some vaccines with an average follow-up time for each participant of a few months.

Perhaps the most ground-breaking novelty in the development paradigm of COVID vaccines was the anticipation of the timing of large-scale production of the vaccine to a phase prior to the marketing authorization of the vaccine itself, an operation with a considerable risk of economic losses in case of failure of the trials in progress (Figure 1).



Modified by: Lurie *et al.*, 2020a

Figure 1. Paradigms for the development of vaccines

The optimization of the development, testing, evaluation, and production time horizon of the vaccine represents an undisputed advantage for the community, since it makes available over a short time large amounts of product for the vaccination of many people.

The current strategies put in place to evaluate the safety of the vaccines, in particular the large number of tested individuals, largely offset the limitations inherent in the speeding up of procedures and lend support to the robustness of the scientific evidence (Kostoff *et al.*, 2020).

The shorter observation time has been offset by the inclusion of very large numbers of participants in the trials, in the order of tens of thousands. Together with the very high incidence of the event (COVID-19 disease, has held sway all over the world since the beginning of 2020), these two measures have made possible to have an adequate number of events as numerator, and a very high amount of person-time as denominator: theoretically, the participation of fifty thousand people observed for an average time of three months produces an overall time of one hundred and fifty thousand person-months equivalent to a follow-up of over six thousand people for two years. Of course, there may be conditions that do not make this equation completely truthful, but the current conditions of a very high incidence may offer such a uniformity of events as to make this type of study approvable.

In light of the above considerations, the race to develop vaccines raises a number of important ethical questions, relating to the novelty of the approach adopted for the development of some vaccines, and the possible effects of the new approach in the long term. Other key issues concern the evaluation of the safety and efficacy of the vaccine in the pre-clinical and clinical phases (Schwartz, 2020; Shah, 2020; Jiang, 2020).

1.3. Assessment of safety and efficacy: from pre-clinical to clinical studies of vaccine candidates

The safety of a medicinal product needs to be considered both in pre- and post-authorization studies. The main consideration to be made about the evaluation of vaccines is that it follows the same rules as for the other categories of medicines. Therefore, assessing the safety of the subjects enrolled in the study remains the primary objective of clinical trials, and in particular, the main focus of Phase 1 - FIH.

To support the progress of vaccine development, pharmacodynamics (PD) studies need to be carried out on predictive animal models, which are called *proof of concept* studies, right from the pre-clinical phase to assess immunogenicity. Based on the type of induced response, it is possible to derive information on the seroconversion rate and on the geometric mean of the antibody titer (WHO, 2005; WHO, 2016a).

The breadth of non-clinical data supporting safety depends on the vaccine construct, the data available for the construct, and the data of closely related products. In particular, the parameters that must necessarily be considered are the relevance of the species (which must be able to develop an immune response that is comparable to that of humans), the type of strain, the dosage schedule (to determine the dose that induces peak antibody production), the method of administration of the vaccine, and the time to evaluate the endpoints. Additional investigations may also be needed to support specific needs such as: i) immunological assessment to investigate the mechanism of an effect observed following administration of the vaccine; ii) studies on the biodistribution of the constructs; iii) developmental toxicity studies if the target population includes pregnant women and childbearing potential; and iv) genotoxicity and carcinogenicity studies, for particular vaccine components such as new adjuvants and additives.

Decisive pre-clinical considerations of a regulatory nature regarding the development of the vaccine for the treatment of COVID-19 emerged during the first workshop held on March 18, 2020 of the international

coalition of representatives of regulatory agencies from around the world[1], the *International Coalition of Medicines Regulatory Authorities* (ICMRA) (http://www.icmra.info/drupal/en) (ICMRA, 2020a), during which special emphasis was placed on the following two key topics:

1. Preclinical data required to support proceeding to FIH clinical trials.

   In order to speed up the development of a COVID-19 vaccine produced using a platform already in use, all the knowledge accumulated on the technology in question needs to be exploited. Hence, in order to start the clinical trials on the candidate construct, if a platform technology utilized to manufacture a licensed vaccine or other investigational vaccines is well characterized, it is possible to use toxicology and clinical data accrued with other products using the same platform, and all the relevant CMC (Chemistry, Manufacturing and Control) characterization to support quality and safety needs to be adopted. The vaccine manufacturer must therefore provide justification demonstrating that certain pre-clinical studies, such as toxicology studies, need not be carried out before starting the clinical FIH trials. The experts of the regulatory authorities also agree on the possibility of carrying out evaluations of the efficacy of COVID-19 vaccines, in parallel with the clinical development, in validated pre-clinical models exposed to viral challenge (studies that are based on an intentional infection induced in the animal that is exposed to the virus in order to study the protective effect of the administered vaccine), in accordance with a strong rationale justified by *in vitro* data and by studies aimed at characterizing at least the immune response induced by the vaccine candidate in the animals (ICMRA, 2020a).

2. Need to address the theoretical risk for SARS-CoV-2 vaccine-induced disease enhancement prior to proceeding to FIH clinical trials (a phenomenon called Antibody Dependent Enhancement, ADE).

   In consideration of the urgency of carrying out FIH studies on the candidate vaccine, the ICMRA regulators all agree on the importance of adopting risk mitigation strategies in the administration of the vaccine. In fact, it is possible that a greater severity of symptoms may occur due to ADE, a phenomenon that was observed with the vaccines against Dengue, MERS, and SARS. Although there are limitations in current knowledge and understanding of the risk of escalation, the ADE effect is an obstacle in the development of the candidate vaccine, a special circumstance that must be assessed on the basis of available scientific knowledge which may include the use of relevant animal models currently under development. Studies on animal models are considered equally important for understanding this potential induced risk; however, we need to acknowledge that, among the experimental models currently available and relevant for COVID-19, there is a limited availability of non-human primates and that it is not possible to request such studies for every COVID-19 candidate vaccine prior to initiation of FIH trials, thereby significantly delaying clinical development (ICMRA, 2020a).

Although not unanimous, regulators still agree that some vaccine constructs, for which there is adequate support from knowledge of the elicited immune response, may be allowed to proceed with FIH studies without first completing the animal studies to assess the potential risk of increase in the disease by implementing adequate risk mitigation strategies. In case FIH clinical studies are allowed to proceed in the absence of pre-clinical studies, the latter should be conducted in parallel with the clinical trials so that data becomes available before enrolling large numbers of subjects in Phases 2 and 3.

Risk mitigation strategies to be considered for the FIH clinical trials include enrolment of healthy young adults, adequate informed consent to be sure that participants are aware of the theoretical risks, careful follow-up on safety, and frequent monitoring.

[1] On the role of ICMRA see also par. 2.1.1.

The continuous evolution of the emergency context requires that the decisions taken are constantly updated; indeed, at the second ICMRA workshop held in July 2020 (ICMRA, 2020b), the need to have the following information was confirmed: i) non-clinical data characterizing the immune response induced by the vaccine, derived from studies on animal models vaccinated with clinically relevant doses of the COVID-19 candidate vaccine; ii) assessment of the immune markers of Enhanced Respiratory Disease (ERD).

To date, preliminary data from animal models show no evidence of an ERD risk, although further data on this issue is expected to be available shortly. In general, the transition to Phase 3 clinical trials is determined on a case-by-case basis and depends on the specific construct of the COVID-19 vaccine and on the totality of pre-clinical and clinical data available for the construct (ICMRA, 2020b).

1.4. Safety and efficacy assessment in clinical trials

Following the pre-clinical phase and the Phase 1 (FIH) and Phase 2 trials, aimed at assessing the tolerability and safety of the product and at defining the most appropriate doses and vaccination schedule, the Phase 3 can offer reliable information on the efficacy to support decisions in the regulatory, clinical, and public health fields.

1.4.1. Target populations

Safety and efficacy evaluation of the COVID-19 vaccine in the late stage of the clinical development should include several population groups, as to ensure that vaccines are safe and effective in all subgroups designated as the future beneficiaries of the vaccine (EMEA 2007; FDA, 2020a). In particular, the following should be guaranteed:

- adequate representation of elderly subjects and individuals with comorbidities;
- representation of different ethnic groups;
- representation of the paediatric population;

Developmental programs are also encouraged as they could support the inclusion of pregnant women and childbearing potential who are not actively avoiding pregnancy.

Although Phase 3 studies are designed to evaluate the efficacy in the overall population, since they do not have a statistical power to demonstrate the efficacy in particular subgroups, it is important to verify that the effect of the vaccine is consistent across subgroups of participants, especially by age classes and risk levels.

The categories considered at greatest risk of severe COVID-19 disease progression are the elderly ≥65 years of age and those with comorbidities such as diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, and HIV infection.

1.4.2. Outcomes or Endpoints

The choice of the outcomes under study has been widely debated together with the duration of the observation time needed to intercept the most serious forms of the disease. In general, the endpoints of Phase 3 studies include both protection from infection and from the disease, achieved through humoral (specific and neutralizing antibodies) and cellular (CD4+ and CD8+ T lymphocytes) immunity, involving different age groups and population characteristics (EMEA, 2007). The primary endpoint in each study must be carefully selected in accordance with the proposed indications.

In a clinical trial, the primary endpoint is expected to provide the most important clinical evidence directly related to the primary objective of the study, and it is also used to estimate the sample size. The choice of the primary endpoint affects not only the duration of the trial but also the future application of the study results from a public health perspective. The secondary outcomes are supportive measurements related to the primary objective and are in any case relevant.

In the case of COVID-19 vaccines, EMA (European Medicines Agency) indicates the laboratory-confirmed COVID-19 disease of any degree of severity as the primary endpoint to assess preventive efficacy, i.e., the capacity of the vaccine to prevent symptomatic and clinically evident infections. It also recommends collecting sufficient information to assess the efficacy against severe forms of COVID-19 (EMA, 2020a). Along the same lines is the FDA (Food and Drug Administration), which however offers a certain degree of discretion in the choice, and it includes laboratory-confirmed SARS-CoV-2 infection as an acceptable primary endpoint. FDA gives a case definition for mild, moderate and severe forms of the disease according to a list of signs and symptoms, with the aim of harmonize future comparative studies on the efficacy of different vaccines (FDA, 2020a). This issue is also included in the ICMRA guidelines (ICMRA, 2020b).

Currently, the presence of specific antibodies against SARS-CoV-2 is considered a marker of exposure, but not necessarily of protection. Indeed, it is not yet clear what titre of neutralizing antibodies is sufficient to provide protection against the infection or the disease. Therefore, although the evaluation of immunogenicity is an essential component in the development of a vaccine, the goal of development programs remains direct evidence of the vaccine's efficacy in protecting against the disease (Mehrotra *et al.*, 2020).

The primary efficacy analysis should be limited to participants who were seronegative for the virus at baseline, as it is important to demonstrate that the vaccine protects individuals not previously exposed to the virus (EMA, 2020a; FDA, 2020a). Secondary efficacy analysis should include an estimate of the protection against the symptomatic disease in participants regardless they were seronegative or seropositive for SARS-CoV-2 at baseline. The studies should also evaluate the efficacy of the vaccine against severe disease, and collect data on asymptomatic subjects providing an estimate of the prevention from infection.

EMA and FDA guidelines recommend that the success criteria for vaccine approval be an estimated reduction in the primary endpoint of at least 50% in the vaccinated group compared to the placebo group (1- Relative Risk percent), with a lower limit of the 95% confidence interval of at least 30% (EMA, 2020a; FDA, 2020a).

1.4.3. Duration of follow-up and monitoring of adverse events

A limit of the trials for the development of COVID-19 vaccines is the lack of long-term safety and efficacy data as well as the difficulty in acquiring information on other important outcomes such as serious forms of the disease, hospitalization, mortality, and efficacy in some subgroups (e.g., elderly people for whom recruitment is more difficult); these data can be gathered at a later stage, after approval.

It is essential continuing to collect data on COVID-19 vaccine also after the marketing authorization. Indeed, monitoring vaccinated individuals will allow to confirm or not the efficacy estimates, to follow the persistence of immunity and obtain further follow-up on the vaccine safety, in a continuous assessment of the benefit/risk ratio.

The assessment of the safety of a vaccine during clinical development includes monitoring for expected local and systemic adverse reactions (reactogenicity) and unexpected adverse events (EMEA, 1995). Safety data are collected after each vaccine dose and during the follow-up period after the administration of the

last dose, for at least 1 year (preferably 2 years), in order to identify events that might occur in the long-term (EMA, 2020a; FDA, 2020a).

In case of COVID-19 vaccines, a median follow-up time of at least 2 months after completion of the vaccination regimen is recommended, allowing for the identification of potential adverse events that do not occur in the immediate post-vaccination period (Krause *et al.*, 2020a).

Data from pre-authorization studies should usually be sufficient to reliably determine the frequency of uncommon local and systemic adverse reactions, i.e., reactions occurring with a frequency between 1/100 and 1/1000 in vaccinated persons. Differences in the safety profile could be observed in some target subpopulations, therefore it may be necessary to gather data of uncommon adverse events in various subgroups before the marketing authorization.

In a context where the approval of a new COVID-19 vaccine is urgent, several critical aspects may arise in the absence of adequate follow-up: efficacy data that are not robust, low power of the trial in identifying uncommon adverse events, lack of long-term safety data (e.g., autoimmune diseases and neurological syndromes, antibody-mediated disease enhancement), lack of knowledge about the duration of the immune response which should protect from the disease. ICMRA has recommended that the ongoing studies should continue the follow-up as initially planned in the protocols (for at least one year or more) and that the evaluation of randomized subjects in the group receiving the vaccination and in the respective control group be continued as long as possible (ICMRA, 2020c).

The pharmacovigilance system in place in the European Union will be used to promptly collect and report data on adverse reactions during the vaccination campaign. In addition, a risk management plan has been developed for post-approval monitoring and active safety surveillance, so that the EMA can act as quickly as possible if an alert is detected. In Italy, in the COVID-19 context the surveillance system becomes an active monitoring tool for the evaluation of the side effects over time , through the establishment at the Agenzia Italiana del Farmaco (AIFA, Italian Medicines Agency) of an *ad hoc* Scientific Committee for the post-marketing monitoring of COVID-19 vaccines (https://www.aifa.gov.it/en/-/l-aifa-istituisce-il-comitato-scientifico-per-la-sorveglianza-dei-vaccini-covid-19).

The pharmacovigilance activity of AIFA has led to the first pharmacovigilance report on COVID-19 vaccines, which will now become a monthly report (https://www.aifa.gov.it/en/-/primo-rapporto-aifa-sulla-sorveglianza-dei-vaccini-covid-19).

Regarding the duration of the immune response induced by the natural SARS-CoV-2 infection, in the absence of definitive experimental or clinical data, which necessarily require longer time to be consolidated, only hypotheses based on previous experiences with other endemic coronaviruses and with SARS-CoV-1 and MERS-CoV can be formulated.

Experimental, serological and sero-epidemiological studies suggest that coronaviruses, including SARS-CoV-2, induce neutralizing and protective antibodies, but the antibody-mediated protection may be short-lived (a few months, especially in asymptomatic subjects), while cellular immune responses, also to other coronaviruses, are less known. All this could generate the phenomenon of re-infection in individuals who have recovered from COVID-19, and also in case of vaccinated individuals, so that a specific boost could be needed in the vaccination strategy with a timing that could depend also from the global trend of the epidemic.

In other vaccines, as those against malaria and seasonal flu, post-marketing experimental and observational studies have showed decreased efficacy over time from the disease protection (RTS, 2015; Ferdinands, 2017).

Observational studies carried out during the vaccination campaign will be important to better understand long-term protection and safety. In this regard, EMA is collaborating with ECDC (European Centre for Disease Prevention and Control) and Member States for the implementation of a European network that will conduct surveillance studies on safety and effectiveness.

2. Legal and regulatory aspects

Key points

- It is also thanks to the momentum given by the *International Coalition of Medicines Regulatory Authorities* (ICMRA), the regulatory agencies of the European Union, of the United States and of many other jurisdictions have taken steps to speed up the development, manufacturing and deployment of safe and effective vaccines.
- Measures have been taken also in Italy to speed up the authorization procedures for starting clinical trials concerning COVID-19.
- At the present time, in Italy, the new studies on COVID-19 are evaluated at first by the Technical Scientific Board (CTS) of the Italian Medicines Agency (AIFA). Subsequently they are evaluated by the Clinical Trials Office of AIFA and, finally, by the Ethics Committee of the Lazzaro Spallanzani National Institute of Infectious Diseases.

2.1. Technical scenario in an emergency context: harmonization and international cooperation

2.1.1. Cooperation among Regulatory Agencies and the role of ICMRA

There has always been cooperation among international regulatory agencies, but following the foundation of the aforementioned International Coalition of Medicines Regulatory Authorities (ICMRA) in 2012, an international coalition of representatives from regulatory agencies around the world was established, whose aim is to address current and emerging human medicine regulatory and safety challenges, strategically and in an on-going, transparent, authoritative, and institutional manner (http://www.icmra.info/drupal/en).

The dramatic scenario that has arisen following the advent of SARS-CoV-2 has led to an even greater need for communication and discussion among international regulatory bodies, since the challenge being faced is common to all. In this context, the activity of ICMRA has focused on the definition of mechanisms intended to harmonize the regulatory and decision-making processes with the aim of accelerating and simplifying the development, authorization and availability of treatments and vaccines for COVID-19 at the global level.

In line with the indications set forth by ICMRA, many countries have adopted flexible regulatory mechanisms aimed at optimizing the authorization procedures for the vaccines under study that have sound evidence in terms of safety and efficacy.

2.1.2. Procedures adopted in Europe

In order to guarantee access to safe and effective vaccines throughout Europe, the European Commission has promoted, from the outset, a coordinated approach to vaccination strategies, described in the Communication "EU Strategy for COVID-19 vaccines" (https: //eur-lex.europa.eu/legal-content/IT/TXT/?qid=1597339415327&uri=CELEX:52020DC0245) of 17 June 2020. One of the two lines of action indicated in the document concerns the adaptation of the European Union's regulatory framework to the current emergency and making use of existing regulatory flexibility to accelerate the development, authorization, and availability of vaccines while maintaining the standards for vaccine quality, safety, and

efficacy. As stated in the Communication, “whilst the need for a vaccine is urgent, it is essential that any regulatory decision concerning its authorization is underpinned by sufficiently robust data to ensure patient safety and vaccine efficacy. The EU’s regulatory framework, which offers a high degree of protection, contains regulatory flexibilities to cater for urgency”.

The criteria adopted by the European Commission to decide which vaccine manufacturers are to be given support, include not only the speed and ability to provide doses in sufficient quantities by 2021, but also robustness of their scientific approach and of the technology used.

The Commission has thus established a procedure for procurement and support in favour of the development of experimental vaccines: manufacturers who have started or are about to start a clinical trial must notify the Commission. The latter will conclude advance purchase agreements with producers on behalf of the Member States: in return for the right to buy a specified number of vaccine doses in a given timeframe and at a given price, part of the upfront costs faced by vaccine producers will be financed from the Emergency Support Instrument. This intervention in support of manufacturers will reduce their risks and shorten the production timeline.

Member States as well are involved in the procedure right from the beginning, by participating in the choice of the experimental vaccines: indeed, the experts and representatives of Member States sit on the Steering Committee which assists the Commission by formulating guidelines and by providing advice on the aspects related to the conclusion of the preliminary purchase agreements.

With a view to flexibility, Regulation (EU) 2020/1043 (Europe, 2020) of the European Parliament and of the Council of 15 July 2020 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19) has been adopted. The Regulation provides for a temporary derogation from certain rules, with reference to clinical trials relating to medicinal products containing or consisting of genetically modified organisms: in particular, a derogation is allowed from Directive 2001/18 / EC in that applicants are not obliged to include a copy of the competent authority’s written consent to the deliberate release of genetically modified organisms into the environment, and of Directive 2009/41 / EC, on the contained use of genetically modified microorganisms, carry out studies with prospective follow-up for an adequate amount of time.

At the same time, EMA’s action plan for emerging health threats was activated in Europe and subsequently each Member State implemented its own individual strategies designed to contain the spread of the epidemic as much as possible (EMA, 2018).

At central level, in pursuance of Decision 1082/2013/EU (Europe, 2013), EMA set up a Task Force (COVID-ETF) (EMA, 2020b) with the aim of intervening in the event of an emerging threat to human health by coordinating actions focusing on the development, authorization and surveillance of all the medicinal products authorized in the EU to address the health threat.

The main objective of the COVID-ETF is to draw on the experience of the European medicine regulation network and ensure a rapid and coordinated response to the COVID-19 pandemic through the efficient management of product review activities and the timely production of supporting data.

For all of its activities the task force reports directly to EMA’s Committee for Medicinal Products for Human Use (CHMP). Strict rules are in place to ensure the independence of all of its members. The COVID-ETF is chaired by the EMA and composed of the Chair and Vice-Chair of the CHMP, the Agency’s Safety Committee (Pharmacovigilance Risk Assessment Committee, PRAC), the Paediatric Committee (PDCO) and relevant working groups, as well as the Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh) and the Clinical Trials Facilitation Group (CTFG). It includes CHMP

rapporteurs and co-rapporteurs for all COVID-19 medicines and vaccines, as well as additional experts as needed, including those involved in reviewing applications received at the national level (EMA, 2020c).

In relation to vaccines, antivirals and other medicines intended for the treatment or prevention of COVID-19, the tasks of the COVID-ETF are as follows:

- review the available scientific data on medicines for the treatment of COVID-19 and identify promising candidates;
- review protocols and provide comments on the development plans to manufactures developing COVID-19 medicines, when it is not possible to promptly receive formal scientific advice;
- provide scientific support in collaboration with the CTFG to facilitate clinical trials conducted in the European Union for the most promising candidate medicines for COVID-19;
- prepare specific scientific position papers and provide input for public disclosure;
- interact and cooperate with stakeholders.

The **assessment procedures** prepared by EMA for the pandemic context concern the rapid procedure called Fast-Track which envisages:

1. rapid ***scientific advice***, an ad hoc procedure for obtaining robust preliminary scientific evidence in support of the correct progress of studies (<20 days vs. 40-70 days normally required);
2. rapid agreement of a paediatric investigation plan by the Pediatric Committee (PDCO), which in collaboration with international regulatory authorities such as the FDA, assesses paediatric studies in consideration of their complexity (≥20 days vs. < 120 days normally required);
3. use of the ***Rolling Review*** (RR) tool which allows EMA to continuously assess the data for an upcoming highly promising application as they become available.. This is one of the most important regulatory tools that the EMA has put in place to speed up the assessment of a promising drug or vaccine during a public health emergency. Normally, all data on the efficacy, safety and quality of a medicinal product and all required documents are to be presented in complete form at the beginning of the assessment in a formal application for marketing authorization. In the case of a progressive Rolling Review, the CHMP of the EMA reviews the data as they become available from ongoing studies in subsequent review cycles, before a formal application is submitted. Once the CHMP decides that the available data are sufficient, the proposer submits the formal application. By reviewing the data as they become available, the CHMP can express its opinion on whether or not to authorize the medicinal product or vaccine at an earlier date. The RR continues until sufficient evidence is available to support a formal application for marketing authorization. EMA completes its assessment in accordance with its usual standards of quality, safety and efficacy (review cycles of approximately 14 days based on the amount of data);
4. **accelerated assessment**, is a procedure that enables EMA to evaluate applications for the authorization of a product that is of great interest to public health when urgent action is required; it reduces the timeframe for review of an application for marketing authorisation for medicines of major public health interest when the RR procedure is not applicable. Assessment times are reduced to an absolute minimum (<150 days vs. 210 days envisaged by the standard procedure, net of the time Companies take to respond to queries). In the case of pandemic vaccines, to date only RR procedures have been applied.

Other important regulatory tools promoted by EMA in the context of the COVID emergency are:

- possibility of requesting an **extension of the indications for use** (line extension) through the methods envisaged for products already authorized that can be re-proposed for the treatment of COVID-19 subject to motivation of the impact on public health by the owner of the Marketing Authorization (AIC);

- obtaining a **conditional marketing authorization** in the event that the CHMP considers that the risk / benefit ratio of the product is favourable and that medical needs are met in the interest of public health with immediate availability on the market and a mature dossier is available within 1 year;
- possibility of applying **compassionate use programs** to make unauthorized medicines available at national level;
- use of the **PRIME modality** (Priority Medicine) for receiving advanced and early support for the development of treatments or vaccines for COVID-19 (EMA, 2020d).

2.1.3. Procedures adopted in the USA

In the USA, the regulatory tools for overcoming the criticalities related to regulatory approval envisage a public-private partnership that has been devised to speed up therapeutic interventions and the development of vaccines for the treatment of COVID-19 and is represented by a strategy called ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines).

ACTIV comprises four areas of interest, each of which is headed by a working group of scientists representing the government, industry and the academic world:

a) standardize and share pre-clinical assessment methods for comparison and validation;

b) prioritize and accelerate the clinical assessment of the therapeutic candidates with the greatest potential;

c) maximize the capacity and effectiveness of clinical trials by linking together existing clinical trial networks;

d) creation of a collaborative network to share information on natural immunity and the immune response induced by the candidate vaccine using innovative tools.

In the epidemic context, the FDA has provided for the possibility of an "Emergency Use Authorization" (EUA) (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory- and-policy-framework / emergency-use-authorization). This mechanism facilitates the availability of medical countermeasures, including vaccines, during a public health emergency. The FDA can therefore grant the use of products that have not yet been officially approved or have been approved for uses other than the diagnosis, treatment and prevention of COVID-19.

The issuance of an EUA is different from the traditional FDA authorization process as it does not represent an approval; the EUA is requested by the manufacturer and the concession follows the evaluation of all the available scientific evidence by the Competent Authority which assesses its effectiveness and any known or potential risks and benefits. If the product meets the standards of efficacy and has a favourable risk / benefit ratio, it will be made available during the emergency. The EUA requires that the clinical data be constantly updated with a view to obtaining official approval (https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained).

It has been pointed out that, following an EUA, there is no clear policy regarding the reassessment and modification of these decisions, with the ensuing need for a system to carefully monitor the safety and efficacy of the vaccine even after approval (Avorn *et al.*, 2020).

2.1.4. Procedures adopted by the World Health Organization

Globally, on 31 December 2020 the World Health Organization (WHO) put the "Comirnaty" COVID-19 mRNA vaccine on the list for emergency use (Emergency Use Listing procedure EUL) (WHO, 2020a). This vaccine was developed and is manufactured by Pfizer / BioNTech and it was the first to receive this type of

validation. This act enables countries that do not have their own regulatory authorities or rigorous means for evaluating vaccines, to speed up their approval processes and set up programs that will allow the population to have equitable access to vaccination. This is particularly significant for fostering global access to COVID-19 vaccination.

The EUL procedure involves constant assessment of the data obtained from Phase 2 and Phase 3 clinical trials and of all substantial additional data on the safety, efficacy and quality of the vaccines and of the product risk management plan (WHO, 2020b).

2.1.5. Procedures adopted in Italy

In Italy, the scenario that characterizes the authorization process of medicines for human use has undergone an inevitable reshaping of the regulatory dynamics, in particular as regards the legislation that regulates the organizations belonging to AIFA and to the National Institute of Health (ISS) (two bodies that work in synergy) and the role of the ethics committees and their respective competences (https://aifa.gov.it/sperimentazioni-cliniche-covid-19).

Article 17 of the "Cura Italia" decree-law no. 18 of 17 March 2020 (Italy, 2020a), amended the procedures for assessing and approving the Clinical Trials on drugs for the treatment of COVID-19 and it entrusted the aforementioned task to AIFA. In particular, the procedure envisages that the study protocols be evaluated at first by the Technical Scientific Board (CTS) of AIFA and subsequently approved by the Agency (Clinical Trials Office).

The Ethics Committee of the Lazzaro Spallanzani National Institute for Infectious Diseases of Rome has also been attributed the role of **National Ethics Committee** for assessing clinical trials on medicines for human use and medical devices for patients with COVID-19.

Decree-Law no. 23,issued on 8 April 2020: Article 40 (Italy, 2020b), empowers the CTS to make preliminary evaluations also of **observational studies** on drugs (i.e., "studies relating to drugs used in normal clinical practice in accordance with the authorized indications"), of **programs for compassionate therapeutic use** (that is, the "programs presented by a pharmaceutical company for the use of medicines in the context of compassionate use in multiple patients, based on a predefined clinical protocol which is identical for all patients") and **Phase 1 clinical trials** subject to the acquisition, for the latter, of a favourable opinion of the Phase I Commission at ISS (Italy, 2001b) in continuity with the role it plays pursuant to Article 7 of Presidential Decree 439/2001, and in a manner that will remain in force for the duration of the emergency. In this context, through expert groups set up ad hoc within the context of the emergency and in harmony with the European regulators and AIFA, the ISS promotes hearings and issues opinions to Proponents who request them, on the therapeutic options proposed by the scientific community for the treatment of COVID-19, including vaccines (https://www.iss.it/sperificazione-clinica-di-fase-i).

In the context of the pandemic, the centralization of procedures for the approval of COVID-19 clinical trials has made it possible to reduce the initial extensive of off-label therapeutic drugs by channelling them into clinical protocols with greater guarantees of methodological rigor and ethical prescribing for the patients.

The list of approved trials is constantly updated on the Agency's institutional website (https://aifa.gov.it/sperimentazioni-cliniche-covid-19).

Another important exception concerns the requirements of the current rules for opening up **Centres for Phase 1 clinical trials within the context of COVID-19 infections**. Considering the urgency and importance of Phase 1 trials, with particular reference to those on vaccines, upon proposal of the GCP Inspectorate (Good Clinical Practice), in its Resolution 564/2020 (AIFA, 2020b) AIFA indicated a list of reduced requirements that are to be met by a clinical centre, in order to allow the launch of Phase 1 COVID-19 clinical trials in the largest possible number of healthcare facilities.

Ultimately, the approval process has been streamlined allowing for the approval of projects that have received a favourable opinion from the CTS, AIFA and the Ethics Committee of the Lazzaro Spallanzani Institute in clinical centres that can participate in Phase 1 trials with a reduced number of requirements that in any case are sufficient to guarantee safety. The centres that, in addition to the Lazzaro Spallanzani National Institute for Infectious Diseases of Rome, are involved in the study, are included as satellites and the relevant ethics committees of reference are not formally called upon to express their position, as only the opinion of the National Ethics Committee is valid. The authorization process thus configured has considerably shortened the time required to obtain approval from the Ethics Committees.

3. Ethics criteria for testing COVID-19 vaccines

Key points

- The trials on COVID-19 vaccines are to comply with the ethics criteria that apply to any clinical trial. These criteria are set out in a vast body of documents at both national and international level.
- In pandemic emergencies, the application of some of these criteria may be difficult. Particular attention is needed in balancing the need for rigor in the scientific methodology and respect for ethical criteria. No exceptions are allowed in terms of neither scientific rigour nor ethics.
- The use of placebo is particularly critical. The general rule applies according to which the use of placebo is not allowed when an effective product is available. Exceptions to this rule are admissible only within the limits established in the documents of reference, which include the Declaration of Helsinki.
- In emergency situations, particular attention must also be paid to information, consent, and access to the benefits deriving from the trials.
- In the emergency of the COVID-19 pandemic there are trials in which healthy volunteers are intentionally infected. This practice, which raises serious ethical doubts, could possibly be admissible in some exceptional circumstances, but it is unacceptable in the specific case of COVID-19 vaccine trials.

3.1. General ethics criteria concerning trials

The ultimate goal of developing a COVID-19 vaccine is to eradicate the disease: this means not only protecting the largest possible number of people from the more severe manifestations of SARS-Cov-2, but also breaking the chain of contagion by offering persons the chance to be protected through vaccination.

In the context of a global emergency where the virus continues to circulate, mutate and infect other animal species, the testing of COVID-19 vaccines not only calls on the need for a collective effort, but it points to the fact that the wellbeing of the community requires the contribution and involvement of each individual: every single person can contribute to collective health by taking responsibility for those around him/her.

For their part, the people responsible for evaluating and conducting vaccine trials must always ensure that the individual participants, as well as the community, are the ultimate recipients of the research and not mere instruments for achieving the objectives set out in research protocols.

The primacy of the person over the interest of society is a fundamental pillar of the ethics of research as recognized, for example, in the Declaration of Helsinki of the World Medical Association (Article 8), and by the Convention on Human Rights and Biomedicine of the Council of Europe (Article 3).

This general principle offers the key to interpreting the principles of ethics in research, reported in the plethora of documents produced since the second half of last century by medical and non-medical organizations, both nationally and internationally.

The legal framework of reference, on the international scene, is provided by the actual hard law texts – among which the Convention on Human Rights and Biomedicine (the so-called Oviedo Convention) of 1997

(CoE, 1997) to which Italy also has adhered, even though the instrument of ratification approved by Parliament in 2001 has not yet been deposited (Italy, 2001a) – and texts which, although drawn up within the United Nations, are to be considered soft law and guidelines rather than normative documents, such as the two Declarations adopted by UNESCO (United Nations Educational, Scientific and Cultural Organization) in 1997 (Declaration on the Human Genome and Human Rights) (UNESCO, 1997) and in 2005 (Declaration on Bioethics and Human Rights) (UNESCO, 2005).

There are also regulatory sources that do not have a juridical or political rank, that originated in the scientific and medical field such as the so-called Nuremberg Code (NMT, 1946), which constitutes the historic precedent of the Declaration of Helsinki (WMA, 1964). The ethical and scientific text of reference for trials involving human beings is the Declaration of the World Medical Association (WMA), drawn up in Helsinki in 1964 and subsequently subjected to various revisions and updates, with the latest version being approved in 2013 in Fortaleza.

Besides these documents there are numerous other texts having different regulatory value, such as the well-known "Belmont Report" (1979), of academic origin but of recognized prestige in the international bioethical debate, and above all the "International Ethical Guidelines for Health- related Research Involving Humans", developed by the Council for International Organizations of Medical Sciences (CIOMS, 2019) in collaboration with WHO.

Albeit with considerable differences, there are some recurring principles in these documents that constitute a useful compass, namely: the aforementioned primacy of the wellbeing of the person over the interests of science and society, the freedom of scientific research (under legal provisions that ensure the protection of the human being), the protection of the person in his/her dignity and integrity, maximizing benefits and minimizing risks, respect for autonomy and informed consent, protection of privacy and confidentiality of personal data, protection of vulnerable people, equal access to care, rejection of all forms of discrimination, non-commercialization of the human body and its parts, protection of the integrity of future generations, independent review and respect for justice in transnational research.

Particularly important is the selection of subjects to be included in the trials. The selection process must be fair and closely related to the scientific objectives of the trial and not to other factors. All subjects must be able to participate, without any exclusion, unless there is a proven unfavourable risk-benefit ratio. The exclusion of people considered vulnerable from the trial is contrary to the principle of justice, since it would deprive them of any hope of a cure when no other treatment is available.

In Italy, the same principles have been given the highest juridical ranking since they are enshrined in the Constitution of our Republic. Among such principles, the following are worth mentioning:

- the personal freedom of volunteers and patients (this can be inferred from the contents of Articles 2 and 13 of the Constitution)
- equality and equal dignity of every human being, which requires, especially in the biomedical field, the adoption of selective non-discriminatory criteria (Article 3 of the Constitution);
- the right to health (Article 32 of the Constitution), as a right of the individual and as an interest of the community for promoting the health of the entire population;
- the principle of social solidarity (Article 2 of the Constitution);
- freedom of scientific research (Article 33 of the Constitution);
- freedom of economic initiative of entrepreneurship (Article 41 of the Constitution).

3.2. Ethics of research in emergencies and for COVID-19 vaccines

Within the context of an epidemic, the core ethical requirements of research are substantially the same as those valid in ordinary contexts. However, the circumstances in which the trials take place may create difficulties in applying the principles to the trials under way.

The guideline on research in disaster situations and epidemics in the CIOMS document - International Ethical Guidelines for Health-related Research Involving Humans (CIOMS, 2019) – points out that conducting research in these situations is faced with major challenges such as the need to generate knowledge quickly, maintain public trust and solve practical obstacles that may hinder the implementation of the research. These challenges must be carefully balanced with the need to ensure the scientific validity of the research while complying with ethical principles in its conduct. Researchers, sponsors, international organizations and research ethics committees and other relevant stakeholders should ensure that:

- the trials are designed to produce scientifically valid results;
- participants are selected fairly and adequate justification is provided when particular populations are included or excluded, for example health professionals;
- the potential burdens and benefits of participating in the trial and the possible benefits of the trial are equally distributed;
- individual risks and potential benefits of experimental interventions are realistically identified, especially in the early stages of development;
- communities are actively engaged in the planning of the trials in order to ensure that cultural sensitivities are considered, while recognizing and addressing associated practical challenges;
- the individual informed consent of participants is obtained even in a situation of coercion, unless the conditions for a legitimate waiver of informed consent are met;
- research results are disseminated, data are shared and any actual interventions developed or knowledge generated are made available to the communities involved.

In the specific context of the COVID 19 vaccine research, as already described in the previous chapters, the worldwide expectation of an effective vaccine and the intense clinical, economic and political pressure have led to a revision of the regulatory procedures for COVID-19 vaccine candidates. The exceptional nature of the COVID-19 emergency has also led to consider practices that, under ordinary conditions, would be inadmissible, such as “challenge trials”, in which a group of volunteers is deliberately infected.

3.3. Anti-COVID-19 vaccine efficacy testing and the use of placebo

To date, efficacy tests have been conducted, or are being expedited, on several anti-COVID-19 vaccines, of which some have already received an emergency approval from the regulatory agencies of several Countries.

According to the first FDA indications for anti-COVID-19 developing industries, vaccine trials must always be randomized in double blind and placebo-controlled (FDA, 2020b), but the approval of the first vaccines is likely to determine a change in this requirement, making the use of placebos in the new tests less acceptable.

As it is easier to compare the efficacy of a vaccine against a placebo than against another vaccine, placebo-controlled tests require the involvement of a decidedly smaller number of participants over a shorter period of time, and therefore also a smaller use of resources.

Moreover, placebo-controlled tests make it easier to evaluate the adverse events and avoid the occurrence of confusing effects on the incidence of the disease arising from the intervention of the control group (Kahn *et al.*, 2020).

In this respect, it is advisable to recall the criteria set forth in Articles 33 and 34 of the above-mentioned WMA Declaration of Helsinki (WMA, 1964):

> "Use of placebo – 33: The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
>
> - Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
> - Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option".
>
> "Post-trial Provisions – 34: In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process."

The major objection to the use of placebos emerges if the experimental vaccine is found to be highly efficacious against a deadly disease. In this case, some commentators have argued that researchers would have the "duty to rescue" the participants in a trial by providing them with the vaccine under study. However, this duty still does not apply to clinical trials if the vaccine being tested has not yet been authorised, its efficacy is unproven and there is no effective alternative option (Millum *et al.*, 2018).

Therefore, in the testing of anti-COVID-19 vaccines, the authorisation of a vaccine raises relevant ethical problems for the continuation of the trial already started but also for the design of new trials. As for the trials already started, we could ask ourselves if it is right and legal to continue a blind test or if the people in the placebo control group must be informed of the treatment received or be immediately given the vaccine. In relation to the design of future trials, the problem arises whether or not to provide for a placebo arm when efficacious vaccines are available.

3.3.1. Continuation of ongoing trials

According to Eyal and Lipstich, following the approval of a vaccine, the decision to offer the approved vaccine to all the participants in a trial is incompatible with the likelihood that the trial produce valid results, which is an essential prerequisite in research (Eyal *et al.*, 2020a).

A similar stand was taken by the WHO working group on the evaluation of anti-COVID-19 vaccines (WHO, 2021) according to which, at current conditions, unblinding trial participants wishing to receive an approved experimental vaccine should not constitute an ethical obligation for those in charge of the trial because, once the vaccine is distributed, the observational data obtained from non-randomized trials would give rise to unreliable and misleading results on its safety and efficacy.

Along the same lines, the ICMRA released a *Statement on continuation of vaccine trials* recommending that ongoing trials must continue the follow-up as initially planned in the protocols (for at least one or more years) and that the evaluation of randomized subjects in the vaccinated group and in the respective control group be continued as long as possible (ICMRA, 2020c).

According to those who support the continuation of placebo-controlled trials, in evaluating the benefits and risks of continuation it is necessary to differentiate the purpose of vaccine trials – which are prevention measures – from the purpose of therapeutic trials.

While in a therapeutic trial the participants assigned to the placebo control group – who are sick and do not receive a treatment capable of healing them – are exposed to a risk, in a vaccine trial, the participants assigned to the placebo control group are healthy subjects that receive no protective treatment against a possible infection, thus exposing them only to a possible and theoretical risk equivalent to the contagion that any other subject not participating in a vaccine trial could suffer. Furthermore, in the case of SARS-CoV-2, the participants in a vaccine trial have other instruments with which to protect themselves such as washing their hands, wearing masks, and practicing social distancing.

Lastly, the risk of infection for the participants in the placebo arm could vary according to the level of prevalence and incidence of the virus over a given period of time and to the "herd immunity" effect obtained by administering the vaccine to the participants in the active arm.

A different stand was expressed by several North American bioethicists. According to Christine Grady, for example, if the first results in the study of an anti-COVID-19 candidate vaccine led to its emergency use authorization (EUA), the participants in that trial should be entitled to know if they have received a placebo or an efficacious vaccine, thus making it fair to unblind the trial (Cohen, 2020a).

Of the same opinion is Arthur Caplan who, in the light of several deaths in the placebo control groups of some trials, which could presumably have been avoided if the participants had been given the vaccine, ethically speaking, considers unblinding the trial to be the only possible option, even if this will make a comparison between the different study arms impossible in the long run.

Still according to Caplan, in order to reduce the negative effects, it would be necessary to continue following up the participants after the trial, even if it is not clear if the vaccine manufacturing companies have the means of tracking all the participants who decide to drop out of a study (Weintraub, 2020).

Actually, when safe and efficacious vaccines are used in different countries, paving the way for the universal inoculation, it becomes difficult to ask people to give up the benefits of an available vaccine in order to continue participating in clinical trials or in new studies.

The studies published to date present interim study results and have already been registered through emergency use authorizations.

It therefore appears to be useful and plausible for these studies to be completed according to the approved protocol but without interfering with the inoculation strategies of the country of residence. Therefore, if a participant in a study is called by his/her inoculation service to receive the vaccine, it will be fair to break the assignment code of the trial and invite the participant to dropout if he/she belongs to the placebo arm.

The study will thus be able to continue until the established term, albeit weakened by dropouts.

Ongoing vaccination campaigns will require lengthy timelines in order to cover entire populations, making the probability of extending them to the participants in vaccine trials unlikely for the current year, while the probability will be high for older people and people at risk belonging to the priority groups of vaccination strategies.

3.3.2. Designing new studies

In addition to the initiatives taken by major pharmaceutical and biotech companies, which are supported by relevant public funding from single Countries or at international level, academic groups and the small and

medium-sized companies operating in the sector are advancing at a slower pace and along more conventional lines.

Although the start of a clinical trial for every candidate vaccine can in theory entail an unproductive use of resources, the importance of having a wide range of vaccines – available or being developed – is amply recognized by the scientific community and the concomitant research on different vaccines is considered to be a common advantage for all (Callaway, 2020b).

At the current state of affairs, there are a multitude of aspects that could make a vaccine better than others: the capacity to prevent the onset of more or less serious symptoms, persisting protection over time, the efficacy and safety in different groups (e.g., young and/or old people), low reactogenicity, the required number of doses and especially the capacity to stop the transmission of the infection. Other characteristics that could make a vaccine interesting are logistic factors such as the maintenance of the cold chain.

The presence of several vaccine manufacturers in an epidemic also offers the advantage of assuring greater assurance in the supply chain and hinders the establishment of monopoly conditions with the consequent rise in prices (CEPI, 2019).

For all these reasons combined, it was affirmed that the approval of a first vaccine should not stop research into other potentially better vaccines (Cohen, 2020a).

However, for all the new studies planned there appears to be no other ethically acceptable option than relying on comparative study models between the new products and the approved vaccines.

The new studies on vaccines will be able to progress in different phases and in separate studies or be included in a single comparative study of candidate vaccines, in line, for example, with the proposal made by the WHO research and development group of setting up large international adaptive platform trials for anti-COVID-19 candidate vaccines (WHO, 2020c).

Adaptive platforms for the study of vaccines, which were developed to simultaneously study several vaccines, offer the possibility of starting or interrupting several "arms" of study on the basis of a predefined decision-making algorithm (Angus *et al.*, 2019). Many of these platforms rely on "response-adaptive randomization" rules, which assign the largest number of participants to treatments with more favourable results, providing to cease treatment in case of futility.

3.4. Participation of volunteers and informed consent

The authorization and marketing of the first vaccines inevitably raises difficulties in the continuation of ongoing trials, enabling trial participants to opt out of the study and request to be administered the authorized vaccine.

A possible way of avoiding participant dropout, in case the trial is still ongoing, would be to explain to participants the importance and social value of continuing the study, enabling them to freely choose whether to continue participating in the study in the prospect of receiving the most efficacious vaccine once the trial is over.

At a macro level, the possibility of retaining trial participants will depend on the relationship of trust and transparency that is expected to be established between science and society, while for the specific trials, an essential role will be played by the quality of informed consent obtained at the start of the study and the efficacy of the information received in avoiding the so-called "therapeutic misconception", meaning thereby the participant's false hope in the guaranteed efficacy of the vaccine under study.

In any case, the decision to continue participating in the study must be free and informed and cannot be imposed. For new studies, for the consent to be valid and adequately information-based, it must describe the complexity of the study and include – in addition to information on the experimental nature of the vaccine under study, the known and unknown risks and benefits of the various vaccines, the design of the study and the possibility of receiving a placebo, the available alternative options and the voluntariness of participation – also the possibility of freely dropping out of the study and the possibility that some arms of the vaccines under study be interrupted, including their own, providing an explanation on the possibility of subsequently participating or not in other trials and/or receiving an efficacious vaccine. Informed consent should be dynamic and offer participants the possibility of being updated on the outcome of ongoing studies, including one's own.

Lastly, the decision to continue participating in the study or not will depend on the actual availability of a vaccine in the different Countries and the healthcare systems involved. In a similar scenario, studies might continue more easily in Countries in which approved vaccines are still unavailable.

3.5. Challenge studies

"Human Challenge Studies" (HCS) or "Controlled Human Infections" (CHIs) are clinical studies whose design provides for healthy participants to be intentionally infected with an infective pathogen that can be administered in a variety of ways: in natural, adapted or attenuated form, with lower or higher pathogenicity, or even genetically modified (WHO, 2016b).

These practices marked the beginning of the study of infective diseases as early as the 17th century. An emblematic and well-known episode is when in 1796 Edward Jenner inoculated James Phipps, his gardener's 8-year-old son, with cowpox – giving origin to the term "vaccination", from Latin *vacca-vaccinus* meaning cow – subsequently exposing him to human smallpox, from which the child remained immune.

HCS have enabled the study of different pathologies, including influenza, cholera, dengue and malaria (Roestenberg *et al.*, 2018). It is estimated that from World War II to date, challenge studies have involved roughly 40,000 volunteers in High Income Countries compared to 400 in Low and Middle-Income Countries, where these pathologies are endemic (Jamrozik *et al.*, 2020). HCS are studies marked by "hideous experiments", such as the administration of the hepatitis virus to mentally disabled children at the Willowbrook State School, New York, in the '50s and '60s (Roestenberg *et al.*, 2018), or the experiments on prisoners of war in German and Japanese research programmes during World War II (Jamrozik *et al.*, 2020): it is precisely the Nuremberg trials of the Nazi doctors responsible of committing some of the most atrocious experiments in extermination camps that gave rise to the Nuremberg Code (NMT, 1946) and later to the WMA Declaration of Helsinki as subsequently amended and supplemented (WMA, 1964) in order to regulate research on human beings.

The issue bounced back at the centre of international attention with the COVID-19 pandemic at the end of March 2020, because of the proposal to use this type of study to develop efficacious vaccines against the new coronavirus (Eyal *et al.*, 2020b). Since then, there has been a broad and lively debate on the dedicated literature (Shah *et al.*, 2020a); the WHO proposed ethical HCS criteria for COVID-19 (WHO, 2020d) and *1Daysooner* (https://www.1daysooner.org/), a platform of reference for HCS supporters and volunteers willing to participate, has been created.

Apart from the theoretical debate, to date the only challenge study envisaged for COVID-19 is that relative to a British government project funded with £ 33,600,000, which sets out as its first step to establish the minimum dose of SARS-CoV-2 necessary to induce the infection. The study is conducted in partnership

with the Imperial College of London, hVIVO and the Royal Free London NHS Foundation Trust (Gov.UK, 2020)[2].

Challenge studies may both aim to test vaccines and therapies and to better understand the evolution of the infectious disease and the immune response thereto, especially at its outset (WHO 2020).

As far as the challenge studies for vaccines are concerned, we should recall their difference with respect to normal trials. In both procedures, the volunteers are administered the vaccine to be tested: later, in normal trials, the volunteers are exposed to the natural contagion while in the challenge trial they are intentionally infected. In some HCS designs, several volunteers preliminarily receive different doses of the pathogens with a view to identifying the most adequate one for the following vaccine trial (Eyal, 2020; Callaway, 2020c).

HCS supporters primarily motivate this with the possibility of speeding up the trial period in general and of COVID-19 in particular. This would prove to be extremely important in developing vaccines: it would make it possible to avoid Phase 3 and thus make their authorization faster (Eyal *et al.,* 2020). Indeed, HCS only allow the use of a maximum of roughly 100 volunteers, against the tens of thousands needed for the normal procedure, and require a shorter lapse of time to evaluate the efficacy of the vaccine as it is not necessary to wait for the exposition to occur naturally. Faster processes would facilitate the comparison between several vaccines, thus identifying the more promising one faster than in normal clinical trials, giving decisive indications to subsequently guide the production and distribution processes: a particularly sensitive problem of COVID-19, for which dozens of vaccination strategies compete. Shortening the trial period so significantly not only implies saving a relevant number of lives but also accelerating the lifting of containment measures to limit the spread of the pandemic, thus significantly reducing the relative economic and social costs.

HCS supporters claim that they have a high social value, primarily because of the advantages listed but also because of the increased knowledge of the pathologies studied (Shah *et al.*, 2020b), of the possibility of developing patterns of infection and of the dynamics that these studies trigger, such as, for example, the repercussions on future public health research and practices (Rid *et al.*, 2020).

However, there are some problematic ethical aspects that cannot be separated from the scientific quality of the trials and that go well beyond their social, economic, and political benefits. According to a perspective that distinguishes but does not separate the realm of research from the healthcare dimension of medical activities, when dealing with human beings, the whole HCS method loses legitimacy because the healthy volunteers that are infected are treated as experimental objects, without recognition of their personal dignity. In this perspective, only persisting respect for the therapeutic principle would guarantee the ethics of experimenting on human beings, both in therapeutic and vaccine trials, in compliance with the provisions made in Art. 2 of the Convention on Human Rights and Biomedicine dedicated to the Primacy of the Human Being, that has already been mentioned in this report and which reads: “The interests and welfare of the human being shall prevail over the sole interest of society or science”. In other words, the value of every single human being cannot be sacrificed in the name of collective interests.

Vice versa, admitting a conception of medicine that also includes intentionally risky practices, such as exposing healthy volunteers to little known viruses for which safe and efficacious treatments have not yet been validated, the ethical-scientific debate becomes more articulate. Those in favour of HCS affirm that there are no substantial differences with other trials (Shah *et al.*, 2020a; Steel *et al.*, 2020) or that, at least, there are none between the risks of these studies and the volunteers recruited for Phase 1 of clinical trials in which healthy people are subjected to the trials without receiving direct benefits therefrom (Roestenberg, 2018): the problem is therefore limited to singling out the specific criticalities of HCS, finding a way of

[2] It is dated 17 February 2021, while this report was being finished for publication, news came out of the approval of the UK COVID Challenge study by the Research Ethics Committee, which was specifically established for COVID-19 trials by the United Kingdom Human Research Authority (https://www.gov.uk/government/news/worlds-first-coronavirus-human-challenge-study-receives-ethics-approval-in-the-uk).

reducing them and consequently regulating them. These authors agree on the fact that HCS designs purportedly have a high social value and are ethically acceptable (WHO, 2020d; Shah *et al.*, 2020b) if they feature the following:

a) An adequate scientific rationale;

b) Reasonable risk-benefit ratios: to this end, the risks are to be identified and minimized, making sure that they are made ethically acceptable;

c) Consultation and coordination between Institutions – regulatory, healthcare, political, scientific – as well as involving public opinion;

d) An appropriate selection of trial sites and participants;

e) A rigorous informed consent provision;

f) Proportionality in the retributions.

Summing up, for COVID-19 it would imply recruiting youths with no co-morbidity that, at the current state of knowledge, have a lower mortality rate and a smaller probability of falling ill; volunteers should be isolated for the entire period in which they, being infected, could result to be contagious. These precautions could minimize the personal and social risk, thereby meeting one of the key ethical requirements of testing. Moreover, volunteers should be recruited in Countries in which there exists a high risk of contagion: this would lower the additional risk they would assume by being intentionally infected.

Utmost protection should also be assured to the personnel involved in the trials, including not only healthcare workers but also the researchers working in adequately safe laboratories (*Biosafety Level 3*) to cultivate the viruses to be administered (Deming, 2020). There should also be a maximum availability of therapies for volunteers, should they fall ill. The resources used should not be taken from the ones reserved for the care of infected local populations. HCS supporters compare the volunteers in these trials to living organ donors, to some extent equating the risks and justifying their participation in the trials as a form of "extreme altruism".

On the other hand, those who oppose this type of trials, limiting their arguments to vaccine testing, primarily underscore the inevitably higher risk that volunteers run compared to those enrolled in normal trials. Both classes of trial subjects undoubtedly are exposed to the risk of vaccine testing but challenge trials add to this the risk arising from intentional infection (which could also be provoked through organisms different from the natural one): a natural contagion of the population, and therefore also of those enrolled in traditional testing, might not occur or be more moderate compared to intentional contagion. Intentional contagion therefore requires full awareness on the part of the volunteer, meaning thereby an especially thorough informed consent proportionate to the additional risks. This last requirement is difficult to reconcile with the trial design of a little-known virus for which a validated treatment does not exist.

In addition to the ethical-scientific criticalities raised by the increased risk for patients, the arguments of scholars opposing HCS also include methodological objections. If it is indeed true that the volunteer selection method produces significant advantages because it allows the enrolment of a radically smaller number of persons to be mainly recruited among the younger and healthier population segments (thus proportionally diminishing the risk of exposing a much larger number of volunteers to the risk of a new coronavirus, as would be required in standard double blind clinical trials), it is also true that it is precisely this selection method that could nullify the general validity of results by undermining the primary reason in support of HCS: the selection of such a small number of participants hinders the emergence of infrequent adverse events and the selection of age groups that are less vulnerable to SARS-CoV-2 could disguise the virus's typical dynamics among the older population, invalidating the very usability of trial results and therefore the main reason that would make it advisable to resort to HCS, namely speeding up the testing.

Furthermore, if the reasons in favour of HCS include a greater knowledge of the infection, also with a view to building a model, it is necessary to ask oneself at what point should we start treating the volunteers that eventually fall ill, considering that the early interruption of the disease surely hinders the acquisition of in-depth knowledge of the infection's dynamics. We should ask ourselves where to set the ultimate limit for blocking the course of an intentionally provoked disease. We should also ask ourselves what symptoms, and with what intensity, should appear before activating the therapeutic response. This problem is particularly important for COVID-19, in which many of the people infected are asymptomatic.

In relation to this last aspect, it should be pointed out that in the WHO report on HCS for vaccines, which was published prior to the current pandemic (WHO, 2016b), challenge studies were declared to be ethically admissible whenever a fast and certain system of diagnosing the pathology exists. An additional ethical-scientific acceptability requirement mentioned was the existence of efficacious treatments to cure the disease, prevent significant morbidity and reduce mortality[3]. In its latest report, the WHO (WHO 2020e) instead expressly declares that the existence of specific treatments for an intentionally infected disease is not a reason for of this type of study to be ethically acceptable[4]. This overturns the perspective, contradicting the criteria announced in 2016, undoubtedly prompted by the encroaching pandemic and the slowness and difficulties met in finding efficacious treatments, making it instrumental to those who want to perform challenge trials for COVID-19.

Some instead think that exceptional situations require exceptional responses and, from this perspective, defend the opportunity of using challenge trials for the purpose of developing anti-COVID-19 vaccines (Plotkin, 2020). But it is also true that then, once the emergency is over, it is difficult to avoid that the case of exception turns into a precedent and that some propose to use them also in normal times.

Generally speaking, it is the very design of challenge studies that raises perplexities from an ethical point of view. First of all, insofar as the physician, seeking a treatment for his/her patients, could make them intentionally ill, thus contravening his own professional ethics. Secondly, because it is difficult to avoid the economic issue: the inevitable retribution paid to volunteers is necessarily conspicuous. It is unrealistic for a significant risk like the one potentially intrinsic to HCS, especially in the case of pathogens without efficacious therapies such as SARS-CoV-2, to be run totally gratuitously, with only the refund of expenditures effectively incurred. It should also be considered that the time that each volunteer must invest in the trial is much longer than the time dedicated to standard trials. HCS volunteers, compared to those in standard trials, must be subjected to isolation for the period in which they could remain contagious once they are infected, also taking into account the time needed for the treatment and healing, once the patient falls ill.

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[3] *It is important to note that not all diseases for which vaccines might be developed are suitable for conducting human challenge trials. In many cases, human challenge with a virulent or even an attenuated organism would not be considered ethical or safe. For example, if an organism causes a disease with a high case fatality rate (or there is a long and uncertain latency period) and there are no existing therapies to prevent or ameliorate disease and preclude death, then it would not be appropriate to consider human challenge trials with such an organism. However, a human challenge trial might be considered when the disease an organism causes has an acute onset, can be readily and objectively detected, and existing efficacious treatments (whether curative or palliative) can be administered at an appropriate juncture in disease development to prevent significant morbidity (and eliminate mortality).*

[4] *Although treatment is one important way of reducing risk, the existence of specific, curative treatments is not a necessary condition for the ethical acceptability of challenge studies.* The following is added in a note: *For example, challenge studies are approved and performed for pathogens with no specific treatment (for example, rhinovirus, rotavirus and dengue) as well as for influenza (for which existing antivirals may not always prevent complications of disease, for example myocarditis). Supportive care is provided in all cases.* However, the working group seems to be divided on this point as on the possibility of speeding up vaccine testing, considering that traditional testing on COVID-19 has already started (Cohen, 2020b).

This time should be factored into the retribution paid out, making it more conspicuous than for other trials[5]. Depending on the type of retribution set, this could also lead to an inevitable socio-economic selection of volunteers, which would exacerbate the ethical problem underlying this enrolment method. The retribution paid out risks turning into an incentive for those out of a job: on the other hand, taking leave from work for long and unpredictable periods of time is more difficult for some classes of workers (e.g., self-employed professionals or those in top management positions), making it more likely to enrol socially and economically disadvantaged classes of workers. Consequently, apart from considerations of justice and non-discrimination, this approach could also affect the representativity of the population enrolled.

Lastly, the comparison between living organ donors and HCS volunteers appears to be inappropriate. The former act individually in the intent of saving the life of a real specific person – a family member, an acquaintance or a stranger – diagnosed to need the transplantation of an organ in order to survive for which it is reasonable to predict a positive outcome. The latter instead, must be enrolled in sufficient numbers to implement the trial design in which it is impossible to know the results beforehand: in other words, it is not the decision of the single volunteer that makes the difference but rather the possibility of recruiting a sufficient number of volunteers and the final outcome is not as reasonably predictable and with the same margin of reliability as that for organ transplants. Moreover, a living organ donation is not allowed if it puts the donor's life at risk while in the case of challenge trials, the risk of participants losing their life is less assessable a priori, especially in the presence of pathologies without a specific treatment such as COVID-19.

[5] The retributions indicated amount to approximately £ 4000 for the time employed in the HCS for COVID-19 that are being designed in the UK (E. Callavan, Nature 2020), and to a maximum $ 4000 for influenza vaccines (E. Jamorizik, Springer 2020, p. 72).

4. Points to highlight

In evaluating anti-COVID-19 vaccine trial protocols, research sponsors, ethics committees and regulatory bodies must pay particular attention to several aspects. These have assumed special relevance in the case of anti-COVID-19 vaccine trials, conducted under strong pressure to proceed as quickly as possible, but they also apply in general: some procedures, adopted or designed to respond to the pandemic, are bound to also affect non-COVID-19 trials in post-pandemic times, both from the regulatory point of view (e.g., speeding up evaluation and authorization procedures) and also in terms of the methodological approach (e.g., challenge studies).

4.1. Study design, evaluation, and implementation

Research is ethically acceptable only if it is based on valid scientific methods. Scientifically invalid research exposes participants in the study to unacceptable risks. Ethics committees have the duty to be rigorous on the methodological validity and on the prerequisites of researchers and trial sites.

Shortening the duration of the different phases (design, evaluation, and implementation) of the research expedited in an emergency situation is also desirable in periods of normality, if the quality of the process is maintained high, and should be accompanied by optimizing and, should the case require, increasing the resources allocated to research in terms of personnel, expertise, and infrastructure.

4.2. Risks and potential benefits

Risks must be minimized. 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 reduces 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.

Insofar, as the regulatory procedures adopted for anti-COVID-19 vaccine trials have enabled the approval of new products in a very 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. In this sense, so-called “conditioned approval” mechanisms could be proposed, on the basis of which an approval gained in a shortened time would be re-evaluated after an adequate period.

4.3. Use of a placebo

The gold standard for Phase 3 trials, on drugs as on vaccines, is the design of the placebo-controlled double-blind trial.

Most of the vaccine trials published to date feature a placebo-controlled double-blind design with an average 2-month observation period for large numbers of trial subjects. The emergency approval of vaccines

took into consideration the possibility of acquiring additional precious data on the efficacy (for example on asymptomatic patients) and safety (on rare and serious side-effects), maintaining the observation on all trial participants, including vaccinated and placebo-control subjects.

Phase 3 anti-COVID-19 vaccine studies have already proven a great efficacy in reducing by more than 90% the risk of vaccinated volunteers contracting the disease. This result already deeply affects ongoing studies as well as future ones: when there is a vaccine capable of protecting trial participants, it becomes ethical 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.

4.4. Feasibility

The feasibility dimension, meaning thereby the possibility of conducting and completing a trial, should be analysed in close correlation with the infection incidence factor. In this perspective, a fast-track procedure could benefit from a larger number of patients possibly at serious risk of contracting the infection; a risk that might not persist over time as it is bound to reduce along with the drop in the epidemiological curve.

4.5. Selection of participants

Vulnerable groups must be especially protected. At the same time, they must not be excluded from the possibility of drawing the benefits deriving from the research study recruitment and testing procedures, and all subgroups should be assured adequate representation in vaccine trials. Generally speaking, the population participating in the research, or the subgroup representing it, should be able to draw the benefits derived therefrom.

4.6. Information and consent

Informed consent is the expression of the principle of autonomy and respect for persons. The consent form must be written in such a way as to avoid therapeutic misconception, especially in placebo-controlled trials and in those that compare a vaccine evaluated to be efficacious with a vaccine whose efficacy still remains to be proven.

For trials started on an adaptive platform, in which several vaccines are studied simultaneously with the possibility of starting or stopping the different “arms” under study on the basis of predefined decision-making algorithms and of the interim results achieved[6], the information notice shall describe the complexity of the study and include, in addition to the experimental nature of the vaccine under study, the known and unknown risks and benefits of different vaccines, the study design and the possibility of receiving a placebo, the alternative options available and the voluntariness of participation, also the possibility of dropping out of the

[6] For an in-depth description, please see Par. 3.3.2.

trial and the possibility that some of the vaccine arms under study, including one's own, be interrupted, as well as an explanation on the possibility of subsequently participating or not in other trials and/or of receiving an efficacious vaccine.

It is not justified to include in the trial people incapable of expressing a valid consent insofar as there is the possibility of achieving the objectives of the trial through the participation of people that have this capacity. The general rules for participating in clinical trials also apply to the inclusion of minors.

4.7. Incentives, financial benefits and costs

It is ethically acceptable – and dutiful – to refund participants of any cost incurred that is directly associated with the participation in the trial. However, refunds should never be conducive to disguised forms of payment.

4.8. Impact on the community

Clinical and vaccine trials have an impact on communities. Ethics committees must consider this in order to minimize possible negative fallouts.

It is essential to communicate in simple, transparent, and clear terms what can be realistically expected from the vaccine in terms of efficacy and safety and in what timeframe (including the possibility of unexpected side-effects) in order to keep a dialogue open with the population without fuelling feelings of distrust (which are unfortunately already widespread) in this respect.

4.9. Possibility of generalizing data and results

The production of generalizable knowledge in the full respect of participants is the primary goal of scientific research. Achieving this goal safely and efficaciously, which is essential in the pursuit of a vaccine, is closely connected to the selection of the trial outcomes and of the participants.

The case definition must be as homogeneous and comparable as possible with that of other studies; data gathering procedures must be well described in the protocols. A heterogeneous selection of participants is more likely to assure generalizable data although this approach might not simplify fast-track procedures.

4.10. Dissemination of data and results

In situations in which there is a compelling need to quickly achieve results, it is especially important that the results reported contain appropriate data, be subjected to an independent review and disseminated on scientific magazines: press releases before completing an adequate independent scientific review may not only result to be misleading, but also harmful.

4.11. Economic impact

Accelerating research procedures necessarily imposes dedicating less time to studying and analysing some of the steps. In the worst possible scenario, this could imply investing sizable funds in trials that, as normally happens in research, could turn out to be ineffective or only partially effective.

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Rapporti ISS COVID-19 (ISS COVID-19 Reports)

ISS COVID-19 Reports are mainly addressed to healthcare professionals to cope with different aspects of the COVID pandemic. They provide essential and urgent directions for emergency management and are subject to updates. All reports have an English abstract.
The complete list is available at https://www.iss.it/rapporti-COVID-19.
Some reports (highlighted below) are also translated in English and are available at
https://www.iss.it/rapporti-iss-COVID-19-in-english

2021

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2. Giusti A, Zambri F, Marchetti F, Corsi E, Preziosi J, Sampaolo L, Pizzi E, Taruscio D, Salerno P, Chiantera A, Colacurci N, Davanzo R, Mosca F, Petrini F, Ramenghi L, Vicario M, Villani A, Viora E, Zanetto F, Chapin EM, Donati S. *Indicazioni ad interim per gravidanza, parto, allattamento e cura dei piccolissimi di 0-2 anni in risposta all'emergenza COVID-19. Aggiornamento del Rapporto ISS COVID-19 n. 45/2020. Versione 2 febbraio 2021.* Roma: Istituto Superiore di Sanità; 2021. (Rapporto ISS COVID-19 n. 2/2021). Available also in English.
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7. Torre M, Urakcheeva I, Ciminello E, Aprato A, Favella L, Ferro S, Ercolanoni M, Leoni O, Picus R, Armaroli C, Molinari M, Bachini L, Gemmi F, Germinario C, Moretti B, Allotta A, Boniforti F, Ceccarelli S, Laricchiuta P. *Impatto dell'emergenza COVID-19 sui volumi di attività della chirurgia protesica ortopedica in sette Regioni italiane.* Versione del 17 marzo 2021. Roma: Istituto Superiore di Sanità; 2021. (Rapporto ISS COVID-19 n. 7/2021).

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