Special issue

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. Possible alternatives: re-consent

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

There are many potential benefits of eConsent.

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

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

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

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

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

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

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

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

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

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

8. Clinical trials and patient's vulnerabilities

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

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

treatments, often life-saving measures. It is therefore necessary to outline procedures that, on the one hand, meet the needs of healthcare personnel and patients who are faced with the emergency and, on the other, guarantee the ethical standards of research and patient protection.

The emphasis on the autonomy of patients should take into account the specific vulnerability of Covid-19 patients, experiencing diminished capacity, due to the nature of the symptoms and need for mechanical ventilation and sedation. In addition, the stress of being sick triggers anxiety, and further clouds decision making. Patients frequently make their decisions on participation in trials based on the way information is presented to them verbally, rather than reading a written consent form, and clinicians' time constraints during the pandemic may limit the ability to sufficiently provide this need for patients, further compromising their informed consent. The quality of the informed consent process may be less than optimal.

Covid-19 patients in moderate to severe clinical condition should be considered particularly vulnerable. While full autonomy should be pursued for all patients, early deliberation on the consent process, before any deterioration is notable, should take place. Stressors associated with the pandemic, including social distancing and the likelihood of debilitating symptoms, should be considered. Efforts should be made to conduct a consent process with family members, using advance video technology for those who cannot attend the clinical space. Whenever possible, obtaining consent should be done after limiting unsettling pressures (noise, distracting commotion).

9. Specific vulnerabilities: age, gender, ethnicity

Minors

Minors have been less affected by Covid-19, and when infected become less seriously ill, so that the need for trials was not so urgent as in the adult population. However, some children did develop severe disease. So completely excluding these vulnerable populations from clinical trials, could exclude them from therapies. The risk/benefit calculations of therapies derived from adult trials cannot be readily extrapolated to children. Gaps in our knowledge of pediatric Covid-19 further complicate assessments of risk and benefit. Combined pediatric–adult trials may be a strategy to gather drug efficacy data in children, but it is not clear if these existing trials will have sufficient relevance to analyze efficacy in children specifically[20].

Multicentre coordinated trials should be prioritized. These would support sufficiently powered studies to test therapies for sicker, hospitalized children and facilitate analyses among subgroups with specific predisposing conditions. Existing trial networks like the Pediatric Trial Network could be enlisted. Some therapeutics trials in adults could be extended to include children, as a small number of studies are already doing. Joint studies also would enable resource sharing, alleviating pragmatic barriers to pediatric trials. Children receiving drugs for Covid-19 should at least be offered the opportunity to participate in prospective observational studies. Although these studies are limited in their ability to establish efficacy, they would allow prospective data collection on clinical and virological and drug-associated adverse effects. It would also permit comparative subgroup analyses

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

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

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

Elderly people

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

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

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

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

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

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

Women, pregnant and breastfeeding women

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

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

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

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

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

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

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

Ethnicity

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

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

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

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

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