

Consent concerns in clinical trials of investigational therapies for COVID-19: Vulnerability versus voluntariness

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Abstract

Obtaining informed consent from vulnerable patients participating in clinical trials of investigational therapies for COVID-19 is a major ethical challenge. Ethical and operational considerations – voluntariness, waiver, timing, time, documentation, and responsibilities of the sponsor, the investigator, and the ethics committee – are discussed briefly.

Keywords: Consent, screening, vulnerability, waiver

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INTRODUCTION

Clinical trials of investigational therapies for COVID-19 have caused heated debates about scientific validity of such studies. However, the more important aspect – ethical concerns of participants – is hardly discussed. Experience of Ebola Virus disease clinical trials showed that obtaining valid consent during an epidemic trial is a major challenge.^[1-3] However, published clinical trials of COVID-19 do not discuss difficulties of obtaining informed consent from the participants. This article discusses the issues and the process of obtaining and documenting voluntary informed consent from vulnerable patients participating in clinical trials of investigational therapies for COVID-19.

INFORMED CONSENT PROCESS

Informed consent, a process by which a clinical trial participant voluntarily confirms his or her willingness to participate in a trial, includes:^[4]

1. Disclosure of all relevant information accurately about the nature, purpose, methods, risks, potential benefits, and alternatives available
2. Understanding the information provided and its relevance to her personal clinical situation by the participant
3. Capacity or ability of a participant to make decisions after understanding the information provided and
4. Voluntary decision to participate in clinical trial made without coercion.

VULNERABILITY OF PARTICIPANTS

Understanding of study information among participants in nonemergency or nonpandemic clinical trials is variable.^[5] Comprehension of study design – randomization and placebo-controlled designs – among participants from developed and developing countries is reported to be lower than comprehension of other aspects of a clinical trial.^[4,5] Clinical trial participants from developing countries

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were less likely to refuse to participate or withdraw from a trial and were more likely to be concerned about the consequences of refusal or withdrawal than those from developed countries.^[4,5] This situation becomes more complex for vulnerable patients who are seriously ill with COVID-19 and are in emergency situation.^[6,7]

When a patient suffering from a serious infection is requested to participate in a clinical trial, his vulnerability is likely to cloud his voluntariness. Such patients would be in intensive critical care, receiving high flow oxygen or be on ventilator, and would be worried about complications of disease and death.^[1] Such severely ill patients are vulnerable as their decision-making capacity is impaired, affecting their comprehension of experimental nature of clinical trial, benefits and risks of the investigational drug, and concept of randomization-chance of receiving investigational drug or standard care without any investigational drug. The patient's decision may be influenced by high expectation of benefits and/or low understanding of risks of participation in a clinical drug trial and experimental treatment.^[6,7] This situation is made complex by challenges of language of consent and literacy level, and communication by physicians wearing full personal protective equipment.

WAIVER OF CONSENT

Considering the challenges of obtaining consent in clinical trial during an emergency, the investigator may consider option of waiving or deferring the consent process. However, the rationale of waiver of consent requires strong justification. Ethics committee (EC) 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.^[8] The waiver is usually applicable in emergency-care settings, when patients are not capable of giving informed consent e.g., seizures, sepsis, shock, severe traumatic brain injuries.^[9] However, any proposed waiver of consent in COVID-19 clinical trial is not acceptable as the participants are not incapable of giving consent, benefits of investigational products are uncertain and the risks of adverse reactions of investigational products are real.

TIMING AND TIME

For informed consent, timing of process and time for completing the process are important considerations.

- Timing: Good clinical practice (GCP) guidelines require that prior to participation in a clinical trial,

freely given informed consent should be obtained from each participant. US Food and Drug Administration mandates that informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research

- Time for explaining informed consent document: As per New Drugs and Clinical Trials Rules 2019, the investigator should provide information to the trial subject about the essential elements of the clinical trial as per Table 3 of Third Schedule
- Time for participant: GCP guidelines require that clinical trial participants should be given ample opportunity and time to enquire about the details of the study, to get answers to their questions, and to decide whether or not to participate in the trial.

In clinical trials conducted in nonemergency setting, there is no urgency of screening and randomization. Hence, ample time is available to complete the consent process. However, in COVID-19 patients, there is an urgency of conducting clinical examination and tests to diagnose and treat the disease. Some of the investigations, e.g., liver or renal function test may overlap with screening tests for clinical trial. Medical procedures for diagnosis and treatment of disease can be performed before the consent process for the clinical trial. Standard care, which is usually the control arm, could also be started, without waiting for the consent process to be completed.

The investigator should make efforts to complete the consent process before screening process in as short time as possible, balancing the need for immediate treatment and regulatory/GCP compliance requirements. Clinical/laboratory screening procedures performed solely for the purpose of clinical trial, e.g., pregnancy test, Hepatitis, HIV, and cytokine levels, should be conducted only after the participant has given consent.

DOCUMENTATION OF INFORMED CONSENT

Informed consent documentation requires signature of the participant along with the date and the signature of the investigator. If the patient lacks capacity to give consent due to acute respiratory failure or ventilator treatment, consent may be obtained from a family member or relative acting as the patient's legally acceptable representative (LAR) over mobile phone or E-mail. However, the consent from LAR may not be possible, as they would be quarantined or hospitalized. If written consent is not possible from severe COVID-19 patients or physically isolated patient, documentation of the consent orally or by use of electronic

methods e.g., digital signature is acceptable if approved by the (EC).^[7]

In RECOVERY clinical trial, for patients who lacked capacity to consent due to severe disease requiring ventilation, and for whom an LAR was not available, randomization could be done with consent provided by a treating physician, who was independent of the investigator conducting the clinical trial, and who would act as the legally designated representative. Consent would be obtained from the patient’s LAR or directly from the patient if they recover promptly at the earliest opportunity.^[10] In case the consent from treating physician is not be available during pandemic, and the patient does not recover from the disease, there would be major ethical issues.

Indian regulations require that the investigator should document the procedure of providing information to the participant and his/her understanding of such consent, through audio-video recording. The audio-video recording should capture the informed consent process, verbal consent, signature process, and time of initiation and completion the consent process.

It is important to document refusal or withdrawal of consent in clinical trial in emergency setting. In LOTUS China clinical trial, out of 357 assessed for eligibility, families of 31 patients did not give consent.^[11] In Remdesivir trial, out of 1063 patients, 10 participants or LAR withdrew consent before randomization, and 28 withdrew after randomization.^[11] This information improves credibility of the consent process.

RESPONSIBILITIES OF THE STAKEHOLDERS

When vulnerable patients are included in clinical trials, the sponsors, the investigators, and ECs have special responsibility to safeguard the dignity, rights, safety, wellbeing, privacy, and confidentiality of vulnerable participants [Table 1].^[6]

Informed consent process is the reflection of autonomy and competence of a clinical trial participant. All the stakeholders should make efforts to ensure its sanctity at all stages of clinical trial conduct.

RESPONSIBILITY OF THE SPONSOR

The sponsor should carefully consider the need for inclusion of seriously ill COVID-19 patients. The protocol should discuss the ethical justification for conducting clinical trial in vulnerable population, and describe the process of obtaining informed consent from patients who

Table 1: Responsibilities of stakeholders for vulnerable participants

Sponsor	Justification for inclusion of vulnerable participants Provisions for protecting safety of participants Enable monitoring and quality assurance
Investigator	Recognition of vulnerability Ensure additional safeguards for protection of participants Justification for inclusion of vulnerable participants Address conflict of interest Empower the participant to make decisions Respect dissent from the participant Avoid exploitation/retaliation/reward/credits Well-documented informed consent process Additional safeguards for protection
Ethics committee	Review of justification for inclusion of vulnerable participants Careful examination of risk-benefit, and risk minimization More frequent review and monitoring

may require oxygen or ventilation, or who may undergo special study procedures, and describe special provisions for protecting safety of participants. The sponsor medical and project team should train the investigator and his team in study conduct with special attention to consent process and documentation. Educational material, e.g., interactive formats, electronic tools such as text, graphics, audio, video, etc., would be helpful to the investigators in explaining participant information sheet.

The sponsor should consider COVID-19 trials as high priority for risk-based monitoring. As the participants are enrolled rapidly, remote monitoring of the clinical trial conduct and consent process should be done as soon as 1–2 patients are recruited to ensure that the rights and well-being of participants are protected, and consent documentation is accurate, complete, and verifiable from source documents. The sponsor should audit the trial soon after the enrollment of participants is completed. If audit identifies serious noncompliance, which has the potential to significantly affect human subject protection, reliability of trial results will be under question.

RESPONSIBILITY OF THE INVESTIGATOR

The investigator should be aware of the complexity of conducting clinical trial in an emergency setting and should be prepared to complete the consent process in compliance with regulatory/GCP requirements under time pressure, without support of research team, who may not be attending the site because of fear or hospital restrictions.

The investigator should educate the patients about the clinical trial, benefits and risks of the protocol procedures and investigational product. He should take precautions to avoid exploitation of the patients and obtain consent

without any coercion or incentive for participation. The investigator should empower the participants to make decisions, and respect dissent from them. The informed consent process – audio-video and written – should be well documented. The site should be prepared for audit and regulatory inspection of the clinical trial.

RESPONSIBILITY OF THE ETHICS COMMITTEE

The EC should carefully review justification for inclusion of vulnerable participants, thoroughly assess risk–benefit and risk minimization, and thoroughly scrutinize recruitment process, informed consent document, educational material for participants, and clinical trial agreement/insurance policy, prior to approval of the clinical trial. The EC approval letter should advise the investigator about requirements of additional safeguards for protection of participants.

The EC should frequently monitor the conduct of trial through review of periodic study progress reports from the investigators or monitoring and internal audit reports from the sponsor team. The EC should 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 trial is in compliance to the approval. In case there are major deficiencies in protection of clinical trial participants, the EC should suspend the recruitment or stop the trial. The EC should also monitor when the clinical trial is completed. If monitoring identifies serious noncompliance, the EC should inform the sponsor and the regulatory authorities.

CONCLUSION

Conducting clinical trials of investigational therapy for a pandemic is fraught with ethical challenges of obtaining voluntary informed consent from vulnerable participants. The sponsor, the investigator, and the EC should go extra mile to ensure protection of rights, safety, and well-being of patients participating in high-profile high-impact clinical trials of therapies for COVID-19. In the rush to discover treatments for a serious medical condition, all the

stakeholders should remember that the rights, safety, and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.

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Conflicts of interest

There are no conflicts of interest.

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