Review Article

Redefining informed consent form in cell and gene therapy trials

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Abstract

Informed consent is a foundation of the ethical conduct of research involving human participants. Based on the ethical principle of respect for persons, the goal of informed consent is to ensure that participants are aware of the risks and potential benefits and make a voluntary decision about participating in clinical trial research. The extraordinary scientific advances happening globally, have demonstrated the potential of regenerative therapies in transforming the health of the nation by providing a therapeutic option for diseases that were previously considered incurable. These therapies, which include cells and gene therapy (GT) labeled as Advanced Therapeutic Medicinal Products globally, have complex mechanisms of action. Owing to their highly personalized and intricate nature of these therapies, developing the latter often presents unique challenges above and beyond those encountered for small molecule drugs. We recently looked through some cell and GT clinical trials and realized the lacunae in the informed consent form (ICF) provided by the investigators. Especially in a country like India, where the general understanding and perception of patients is limited regarding clinical trials, it is felt that any lapses in the consent process may jeopardize the informed decision-making and safety of the participants and tarnish the reputation of India globally. The present article highlights the need for appropriate patient and public education on the various aspects of cell and gene therapies and aims to address all the elements of ICF in light of the challenges associated with these innovative therapies.

Keywords: Cell and gene therapy, clinical trial, governance, guidelines, informed consent form, legislation, medical ethics, medical innovation, regulation, transforming healthcare

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Received: 17-11-22, **Revised:** 27-03-23, **Accepted:** 04-04-23, **Published:** 28-07-23.

INTRODUCTION

The National Cancer Institute (NCI) (National Institute of Health [NIH]) Dictionary defines Consent as a process in which patients are given important information, including possible risks and benefits, about a medical procedure or treatment, genetic testing, or a clinical trial. Informed consent is a cornerstone of the ethical conduct of research involving human participants.[1] It rests on the pillars of information disclosure, comprehension, voluntariness, and authorization. Based on the ethical principle of respect for persons, the goal of informed consent is to ensure that participants are aware of the risks and potential benefits and make a voluntary decision about participating in the research. Investigators must follow the International Council on Harmonization good clinical practice guidelines. Its section 1.28 defines informed consent and 2.9 pertains to

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.picr_244_22

How to cite this article: Dalal V, Jotwani G, Yadav ML. Redefining informed consent form in cell and gene therapy trials. Perspect Clin Res 2024;15:4-9.

the ethical requirement of informed consent, while Section 4.8 explains the requirements and process for obtaining informed consent from a clinical trial participant.[1,2] The National Ethical Guidelines for Biomedical and Health Research 2017, as well as the New Drugs and Clinical Trials Rules, 2019 (NDCTR-2019) clearly lay down the need for a template of informed consent which is to be obtained from each human participant before enrolling the patients for the clinical trial. They describe the essential as well as additional elements required in the informed consent form (ICF) for clinical trial participants.[1,3]

India now has 11 ongoing gene therapy (GT) clinical trials and 5 cell-based products for market authorization, with many more in the pipeline. However, they are not without risks and pose complex logistical, economic, ethical, and social challenges for our patients. Another limiting factor is how a patient's judgments could be easily clouded by the lack of known disease burden as well as available treatments (or lack of). The perceived benefits should not minimize the challenges facing patients in understanding the long-term risks and providing valid and meaningful informed consent, whether in a research or clinical setting. However, it is felt that considering the complexity of cell based and gene therapies, greater emphasis needs to be made on the understanding of these modern therapies and the associated risks and benefits to the patients and their families. Especially in a country like India, where the general awareness and perception of patients is limited regarding clinical trials, it is felt that any lapses in the consent process may jeopardize the informed decision-making and safety of the patients and tarnish the reputation of India (the hub of medical tourism) globally.[1,4]

The clinical trial investigators, to begin with, acknowledge that in contrast to the Western countries, India faces more challenges in obtaining informed consent due to the multiplicity of languages, lower level of education, and health literacy because of the larger population. It has been very evident in the literature that despite the undisputed benefits of conducting research, comprehension issues and the lack of basic essential information remains a major obstacle in protecting the rights of future research participants enrolled in clinical trials.[1,5] Keeping this in mind, the ICF/Participant Information Sheet (PIS)/ Participant Information and Consent form (PIC) should be drafted in simple and regional languages without unnecessary legal and technical jargon. The stakeholders should be clearly explained that ICF is not a one-time event but an ongoing process, a process that continues throughout the trial period and beyond, and more than simply consent, it is a process of informed and shared decision making.[1,6] The relationship between a trial investigator and clinical trial participant/patient should be such that the latter may freely contact the former at any time and get all her/his queries resolved [Figure 1]. Therefore, an informed consent approach warrants transparency, education, and engagement taking place over an extended period rather than as a one-off interaction, giving space for answering questions, addressing misconceptions, and allowing participants a cooling-off period for further consent discussions. The stress should be on all-round patient knowledge and comprehension.[6] And equally important factor is the appropriate documentation of the entire process, both on paper as well as on audio and video through recording.

Below mentioned are the elements of an ICF/PIC and the points that need to be taken care of:

Introductory information and purpose

The first and foremost information that should be shared with the participant is the reason they have been asked to enroll and participate in the study. The purpose of the study should be clearly explained emphasizing on the aims and objectives as well as the study duration stressing on its research nature. Any claims of possible therapeutic benefit should be strictly avoided. The aim of this information is to help patients recognize their clinical situation, understand the implications of treatment and integrate every facet of their life into their decision, and understand their role as participants in research. The irreversible nature of these new-generation therapeutics needs to be specifically emphasized and explained to the patients.[4,6] The participants need to be explained about the GT that is going to be used, whether *ex vivo* (genetic modification of cells outside of the body) or *in vivo* (genetic material in the form of DNA applied to alter the genetic repertoire of target cells).

Description of study

This section should include details of the study design and the nature of the gene transfer intervention that is planned. The explanation of the gene transfer technique should be as simple and nontechnical as possible. The unique nature of trial, the use of viral vectors for gene transfer and related information should also be shared. In the case of trials envisaging dose escalation, the basis for the same and its implications should be clearly spelled out. The patient should be given a brief background of the various phases of clinical trials (I to IV) and the phase of the current clinical trial, based on preclinical and clinical evidence. The results of previous trials done with the same/ similar product should also be disclosed to the patient.[3,7]

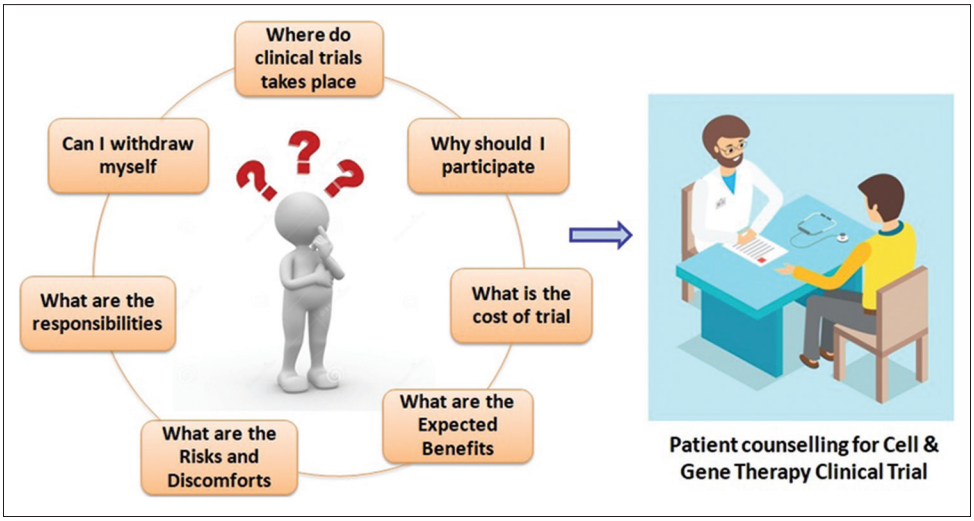

Figure 1: Patient's common questions for cell and GT clinical trials. GT = Gene therapy

Procedures along with the trial treatment schedule

The patient should be made aware of all the study procedures that she/he will need to undergo as a part of the clinical trial. The entire treatment schedule, along with the days of visits for follow-up, should be explained. The probability of random assignment to each treatment protocol in case of randomized trials should also be told. Descriptive clarity should be given regarding the investigational interventions and tests done as a part of the trial vis-a-vis standard treatments for the disease.[1,3,7]

Risks and discomforts

Patients' evaluations of risks and benefits can be greatly affected by the quality and depth of information presented to them. Therefore, detailed information regarding all kinds of probable known or unknown risks, discomforts like logistics, potential side effects, and how these will be addressed and minimized should be clearly mentioned. Any risk of insertional mutagenesis, carcinogenesis, or infection due to the viral vector or transferred gene and its potential to be transferred to the offspring should also be spelled out clearly. In addition, the patient information sheet should clearly enlist the types of adverse events, their severity including death and frequency reported in previous similar clinical trials.[1,8]

Expected benefits

The aim of this section is to help the patient differentiate between receiving standard treatments and participating in the clinical trial. The investigator/sponsor should be careful in conveying the potential benefits of the trial, depending on the phase of the study. Overestimation of therapeutic benefits or underestimated risks of harm, also known as therapeutic misconception, should be addressed by ensuring the balance of the provided information. Emphasis should be placed on the advantages that early-stage trials bring to scientific and medical knowledge, as they have the potential to benefit society.[1,3]

Alternatives

The trial participants should be adequately informed of the standard treatment options available with her/him, which include radiotherapy, chemotherapy, procedures, other drugs, and devices. The patient and public preference for alternative therapies should be valued and they should not be lured into the use of highly expensive but potentially curative treatments instead of cheaper but noncurative treatments.[1,6,8]

Costs

The participants should be provided with detailed information regarding any financial costs that would be borne by the sponsor in the cell and GT trials and their long-term follow-up. The financial considerations should be explained well to the participants/patients.[1,3,8]

Payment for participation

Often, many trials pay human participants for participating in trials. This should be seen with great caution as the poor and vulnerable may give consent in the lure of an additional source of income. The patients should not feel that participating in such trials is a way of getting costly treatment for free.[1]

Compensation for injury

The researcher should ensure free treatment for research-related injury (disability, chronic life-threatening disease, and congenital anomaly or congenital disability) and, if required, payment of compensation over and above medical management by the investigator, institution

or sponsor, as the case may be. The NDCTR 2019 very clearly mentions that in case of any injury, free medical management shall be given as long as required in the opinion of the investigator, and financial compensation shall be provided to the participants by the Sponsors. As per the Draft of New Drugs, Medical Devices and Cosmetics Bill, 2022 (placed in the public domain for public consultation), failure to provide medical management/ compensation shall be punishable with imprisonment.[1,3,5]

Responsibilities of participants

The clinical trials are processes of mutual trust, cooperation, and mutual responsibility involving researchers and participants as researchers take the responsibility of protecting their rights and well-being. Therefore, respecting the researchers is the most vital ethical requirement of the participants. They should be honest about their condition and should regularly report for all follow-up visits and share any side effects or adverse events they experience. As GT has the potential for making permanent changes in the body, long-term follow-up is of paramount importance. Therefore, the participant should always stay connected with the PI/Sponsor and be as committed to the trial as the investigator/sponsor is.[1,3,7,8]

Confidentiality

Understanding the sensitive nature of data collected in these kinds of trials, every effort should be undertaken to protect the privacy of participants and maintain confidentiality. If the trial/study intends to keep the samples or data stored for a long time for use in other research or as a part of creating registry, the investigator/ sponsor needs to employ a separate consent form for the same. Any use of potentially identifying information which may include photographs or videos for publications, can be done only after obtaining explicit permission. Media disclosure regarding any positive developments or adverse events may be done keeping patient's interests in mind.[1,3]

Voluntary participation/withdrawal

The participants should be very well informed that they can refuse to participate in the trial and withdraw their consent at any point in time. The researcher should ensure that the participant can continue to access routine care even in the event of withdrawal of the participant. However, the implications and consequences of withdrawal should be explicitly explained, considering the irreversible course of action of cell and GT. They should be encouraged to return for follow-up even if they withdraw from the trial. As there are chances of vector shedding in the initial phase after giving GT, the participants should be explained the necessary precautions to be taken to minimize the risk to close contacts and family members.[1,6,8]

Assent

Assent is applicable when the trials engage children or persons with impaired decision-making. If their participation in the study is justified, a legally authorized/ acceptable representative needs to give permission on their behalf. All these minor individuals should be approached once they attain the age of eighteen for continued participation and long-term follow-up (LTFU).[1]

Long-term follow up

Novel GT products developed as a result of emerging technologies, such as transposon-based gene insertion and genome editing, also raise concerns for delayed adverse events due to the unique genome-modifying activity of such products. The LTFU period is usually up to 15 years but can vary on a case-to-case basis. The LTFU observations for these novel GT products should be designed to take into account product-specific characteristics, the fundamental and translational knowledge generated in the field, and the product-specific preclinical data generated to facilitate investigational new drug application (IND) studies. The informed consent document must explain the purpose and duration of LTFU observations, the time intervals, and the locations at which you plan to request the participants to have scheduled study visits or be contacted by other means, and details as to what those contacts will involve.[1,9]

Reproductive considerations

The vector employed as vehicles for gene transfer may have the capacity to integrate and cause alterations in the germ line cells. To minimize and avoid this risk, the subject participants are advised to use contraception during the study duration. The inclusion or exclusion of pregnant or lactating women should be clearly mentioned. Conception or pregnancy occurring during the active phase of the clinical trial should be reported immediately to the investigator so that counseling, individual risk-based assessment and long-term monitoring of the child may be done on case to case basis.[1,3,6,8]

Post trial access

A "post-trial access" means making a new drug or IND available to a trial participant after the completion of clinical trial through which the said drug has been found beneficial to the trial participant during the clinical trial, for such period as certified by the investigator and approved by the ethics committee. The posttrial access of the drug should be provided free of cost by the sponsor of the such clinical trial to the trial participants on two conditions. First,

the therapy used in the clinical trial, which has no alternative therapy, has been found beneficial to the participant by the investigator. Second, the trial participant or legal heir of such participant has given consent in writing that the sponsors will have no liability during posttrial use of drug.[1,3]

Process of approvals and clearances

Patients are generally unaware of the timescales and challenges manufacturers face while developing cell therapies and obtaining regulatory approvals.[1,10] They, therefore, need to be clearly explained the procedure to be followed to enroll in a clinical trial, the role of the central licensing authority in approving the trial and monitoring it, and the necessary steps that are required to be taken before the new drug/cell/GT goes for market authorization [Figure 2].

Patient comprehension

Last but the most important aspect of the ICF/PIC is the extent to which the patient understood what was told and explained to him. Studies have suggested that participants may not understand the research they are involved in, nor their rights, even after signing a consent form.[1] Therefore, to make an informed and sound decision, the participants should be given enough time to read and understand the form, ask questions and discuss the same with family members. Language should be simple, with the longer time taken for discussion, counseling, and inclusion of more trained members of the research team for the explanation, if necessary. Effective informed consent relies on a patient's capabilities to understand the information provided on the medical treatments being offered, or the research aims/protocols of a trial, together with alternatives and the risks associated with them [Figure 3]. Factors including age, disease severity, cognitive abilities, and patients affected by mental health conditions or significant psychological suffering, as well as anxiety or denial, may affect a patient's decisional capability. Inadequate understanding of treatment outcomes can lead to differences in patient expectations of therapeutic interventions. What's more, patients' acquisition and application of complex scientific information are further complicated by cultural, linguistic, and health literacy barriers.[1,8,9] Hence, it is important for the researcher to devise novel approaches, such as workshops, games, and street plays, keeping the interest of patients in mind, in order to facilitate their comprehension of their ailment, the treatment options available, and the experimental therapies that are being studied.[2,11] NIH guidelines may be consulted for additional issues related to informed consent.[1,12]

CONCLUSION

To summarize, one size fits all approach can never be applicable to consent forms for such novel therapies. They need to be tailored specifically to each and every study keeping the above-mentioned aspects in mind. In fact, engagement with participants of the trial should begin right at the stage of protocol development. We need to engage patient communities right at the onset to include

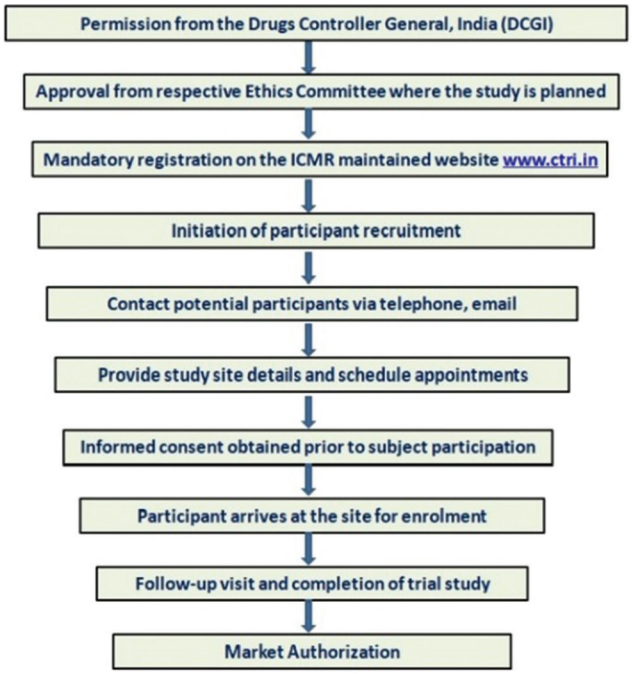

Figure 2: Flow chart for the clinical trial approval process in India

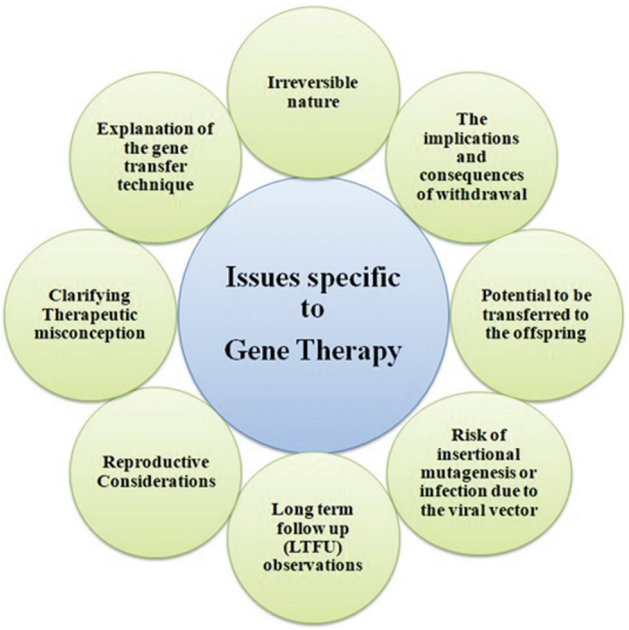

Figure 3: Different important issues related to Gene therapy trials

their insights and feedback into the drug development process. This feedback can help us to make participation in a clinical trial as easy as possible. Individual initiatives should be taken to ensure informed consent practices are genuine and intended within the paradigm of cell and GT. It should be understood that consent is not a one-time event but a continuous process. This should involve a steady interaction with the patients to assess their understanding and as a follow-up improve the consent form.[5,13] Efforts should be made to address the needs and biases of the patients. This can be done by ensuring active engagement with the community as a whole. In addition, the ethics committee overseeing the trial should also include patient experts with a sound understanding of GT to help in leveling the gap between patients and researchers and protect the interest of patients. All these measures can help us in protecting our patients and developing newer therapeutic modalities for them in the long run.

Acknowledgments

The authors faithfully thank the Indian Council of Medical Research, New Delhi, India, for the required support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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