Review Article

National guidelines for gene therapy product (2019): A road-map to gene therapy products development and clinical trials

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Abstract

The "National Guidelines for Gene Therapy Product (GTP) Development and Clinical Trials" prepared by the Indian Council of Medical Research and Department of Biotechnology in 2019 came as a welcome step in the process of regulation of gene therapy research, as there was a lack of Indian guidelines earlier specific to gene therapy. Indian researchers have taken their step in setting the path of gene therapy research, and this guideline serves to provide the standards starting from its development up to translation to new drug including the ethical, scientific, and regulatory requirements to be followed during the conduct of trial. The Indian guidelines were framed with reference to United States-Food and Drug Administration and European Union guidelines on gene therapy. It is the responsibility of all the stakeholders involved in the development of GTP to adhere to the national guidelines. This review provides an outline of the Indian regulatory guidelines on GTP.

Keywords: Gene therapy products, gene therapy, guidelines, Indian Council of Medical Research

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INTRODUCTION

In this rapidly expanding era of biomedical research and appraising burden of genetic disorders, India has become one of the few countries to formulate the guidelines on research involving clinical trials of gene therapy products (GTP). In November 2019, "National Guidelines for GTP Development and Clinical Trials" has been released by the Indian Council of Medical Research (ICMR) in collaboration with Department of Biotechnology (DBT).[1] This document broadly specifies the ethical, scientific, regulatory procedures, and requirements to be followed for developing and conducting clinical trial on GTP in India. The Indian guidelines were framed with reference to (United States-Food and Drug Administration) and European Union guidelines on gene therapy.[2,3] This document provides an overview of the Indian regulatory guidelines on GTP.

INDIAN SCENARIO

Unlike other countries, the prevalence of inherited genetic disorders and its associated morbidity and mortality have not been fully established in India. Based on the data reported from tertiary care hospitals genetic diseases such

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as haemophilia, thalassemia, sickle-cell anaemia, certain forms of muscular dystrophies, retinitis pigmentosa, primary immunodeficiency in children, lysosomal storage disorder, and cystic fibrosis were the most common monogenic genetic disorders affecting the Indian population.[4,5] Despite the growing burden of genetic diseases in India, most of the clinical trials on gene therapy are currently being conducted in other countries such as USA, Europe, and other Asian countries such as China, Japan, and South Korea.[6] Hence, the recently released national guidelines on GTP clinical trials might help to streamline this evolving field of gene therapy which can cater to the large unmet medical needs in Indian patients.

GENE THERAPY AND GENE THERAPY PRODUCTS

Gene therapy refers to the technique of using normal functioning gene to treat a genetic disease either by repairing or replacing or regulating the defective gene. Gene therapy is classified into somatic cell gene therapy and germline gene therapy. In somatic cell gene therapy, the defective genetic material of an individual is corrected by either one of the following methods:

- Introduction of exogenous gene, chimeric, or modifier deoxyribonucleic acid (DNA) sequences which might replace or add to the function of defective gene
- Expression of microribonucleic acid (RNA)-adapted short-hairpin RNA and small interfering RNA
- Gene editing through homologous recombination or by using clustered regularly interspaced short palindromic repeats (CRISPR)-guided Cas9 (CRISPR-associated protein 9) or by other gene-modifying techniques.

Somatic cell gene therapy cannot be transferred to the next generation and the two approaches followed here are *ex vivo* and *in vivo*. In germline gene therapy, the genetically modified cells are transplanted into gametes and vertical transmission occurs here. Due to ethical and social reasons, germline gene therapy is banned in India.

GTP is defined as "a biological substance or therapeutic molecule which could modify the genome, or the extra-genomic DNA or RNA segments (mitochondrial and episomal)." It also encompasses gene modified or edited cells, tissues, organs. GTP consists of a transgene cassette, transgene regulatory systems, vectors or special carriers used for the delivery of nucleic acid and the cellular components. The various *in vivo* and *ex vivo* GTP are listed in Table 1.[7-9]

- Transgene cassette and transgene regulatory systems: This includes the gene of interest (gene which will cause the therapeutic effect), gene editing sequences, and the regulatory sequences which include promoters, polyA, and regulatory factor-binding sequences
- The vector or gene transfer vehicle is the carrier method used for the delivery of nucleic acid to a specific target site, and it can be a biological, physical, or chemical method
- Cellular components are cells or tissues which are modified *ex vivo* and then transferred to target site as a complete GTP.

SCIENTIFIC AND ETHICAL CONSIDERATIONS IN GENE THERAPY

In gene therapy, the new functions and properties mediated by the corrected gene might cause some scientific and ethical concerns. These issues might occur due to the biological and technical complexity faced during the designing, production, and manufacture of GTP.

The precautions which should be followed at the various levels of preclinical and clinical studies of GTP are described below:

- The vector for gene delivery should be selected appropriately depending on the target tissue
- The expression cassette should be designed in a such a way so that only clinically relevant levels must be expressed
- The gene expression should be very specific to avoid unwanted adverse effects and off-target effects in the host.

The factors which might influence the therapeutic efficiency of final GTP are the following:

- The interaction between the vector and host cells and effects of vector uptake into host cells
- The response mediated by the host immune system
- The outcome following the integration of genetic material into host chromosomes
- The levels of transgene expression from the host cells.

The risks which might be encountered with the use GTP are:

- Teratogenicity
- Excessive immune activation
- Introduction of unwanted mutations (e.g., off-target gene editing) or unwanted host-immune response to GTP.

Table 1: Various *in vivo* and *ex vivo* gene therapy products

GTP	Examples or methods
Recombinant viral vectors	Adenovirus
	Retrovirus
	Lentivirus
	Adeno-associated virus
	Herpes simplex virus
	Poxvirus
Nonviral vectors	Naked DNA transfection
	Chemical: Polymer-based delivery, calcium phosphate
	Biolistic: Ultrasound mediated, electroporation
	Lipoplexes polyplexes
	Nanoparticle mediated
Microbial vectors	Recombinant bacteria vectors such as Salmonella, listeria, *E. coli*
Oncolytic viruses	Kill the targeted cancer cells, for example, vesicular stomatitis virus, herpes, reovirus, measles, adenovirus, and vaccinia
Gene-modifying techniques	Short-hairpin RNA
	Small interfering RNA
	CRISPR based
Any of these products- along with a nucleic acid or with any form of genetic material	Soluble or particulate or emulsion or nano-based interventions
	DNA vaccines
	Ex vivo genetically modified cells like gene modified or augmented stem cells, iPS, CAR-T

CRISPR=Clustered regularly interspaced short palindromic repeats, CAR-T=Chimeric antigen receptor t-cells, iPS=Induced pluripotent stem cells, GTP=Gene therapy products

Most of the genetic disorders are chronic and disabling in nature and the need for a cure is the utmost expectation of the affected individuals and their family members. Due to these unmet medical needs, GTP clinical trial advertisements and sponsors should not create false hope about gene therapy among the study participants and their relatives.[10] Germline gene therapy can be misused not only as a performance enhancing method in the field of sports and military but also for selecting specific desired characters in foetus (designer babies). Thus, as explained in the new national GTP guidelines (2019) due to these ethical and social concerns germline gene therapy is banned in India. Further, ICMR national ethical guidelines on biomedical research involving human participants (2017) restricts research to somatic cell gene therapy.[11,12] As per the New Drugs and Clinical trial Rules (2019), GTP is included under the category of new drugs, and academic trials are not applicable to the clinical trials using GTP.[13]

Prior to the development of national guidelines on GTP development and clinical trials, "National Ethical Guidelines for Biomedical and Health Research involving Human Participants 2017" served as a guidance document for dealing with ethical issues involved in the field of human genetic testing and gene therapy research. The national ethical guidelines for human biomedical research 2017 and the national guidelines on GTP development 2019 have been compared based on the salient points specific to gene therapy research [Table 2]. The GTP clinical trials must be conducted following the specific requirements and the general ethical principles mentioned in both these guidance documents.[11]

MECHANISM OF REVIEW-GENE THERAPY ADVISORY AND EVALUATION COMMITTEE COMPOSITION AND FUNCTIONS

Under the guidance of Department of Health Research, Ministry of Health and Family Welfare, Government of India, a multidisciplinary apex body for the research and development in gene therapy, namely gene therapy advisory and evaluation committee (GTAEC) is planned to be constituted, with its secretariat at ICMR. GTAEC will be composed of scientists and clinicians with expertise in gene therapy and with representatives from ICMR, DBT, Central Drugs Standard Control Organisation (CDSCO), Department of Science and Technology, Directorate General of Health Services, and Medical Council of India. The review process for GTP clinical trials protocol is described in Figure 1.

Some of the salient functions of GTAEC are to:

- Guide the sponsors in designing the clinical trial, and it can also provide pre-investigational new drug consultation
- Review the GTP clinical trial applications
- Monitor all the on-going GTP trials
- Collect and archive the GTP clinical trial data to maintain a database
- Periodically review and update GTP guidelines collaborating with CDSCO.

RESPONSIBILITY OF THE STAKEHOLDERS

GTP clinical trials must be conducted only in institutions and hospital with adequate tertiary care facility and by medical

Table 2: Comparison of salient points specific to gene therapy research in national ethical guidelines for human biomedical research 2017 and the national guidelines on gene therapy product development and clinical trials 2019

Specific areas	National ethical guidelines for biomedical and health research involving human participants 2017	National guidelines on gene therapy product development and clinical trials 2019
Gene therapy clinical trial approval and evaluation process	Approval needs to obtained from IEC, DBT, and CDSCO for developing and marketing the products of gene therapy clinical trials	GTAEC will evaluate GTP clinical trial application and will forward to RCGM and CDSCO for final approval. Before initiating the trial, approval from participating IEC has to be obtained
Composition of committee reviewing gene therapy clinical trial applications	The members of IEC reviewing genetic research must have adequate expertise in gene therapy research or the IEC can invite a subject expert for providing opinion on gene therapy clinical trial proposals	GTAEC is a multi-disciplinary apex body composed of scientists and clinicians with expertise in gene therapy and with representatives from ICMR, CDSCO, DBT, DST, DGHS, and MCI. The members of IEC reviewing GTP clinical trial proposals must be updated periodically with advances in field of gene therapy research
Duration of record keeping	After the completion or termination of regulatory clinical trials, the related documents must be archived for 5 years	The institution involved in GTP trials must maintain the pertaining records for a period of 15 years
Follow-up of patients	Long-term surveillance should be provided for all gene therapy trial subjects. Specific duration has not been mentioned	It is recommended to follow up the patients for a period of at least 5 years post-GTP administration and for 10 years post marketing

IEC=Institute ethics committee, CDSCO=Central Drugs Standard Control Organization, GTAEC=Gene Therapy Advisory and Evaluation Committee, RCGM=Review Committee on Genetic Manipulation, DST=Department of Science and Technology, DGHS=Directorate General of Health Services, MCI=Medical Council of India, GTP=Gene therapy products, DBT=Department of Biotechnology, ICMR=Indian Council of Medical Research

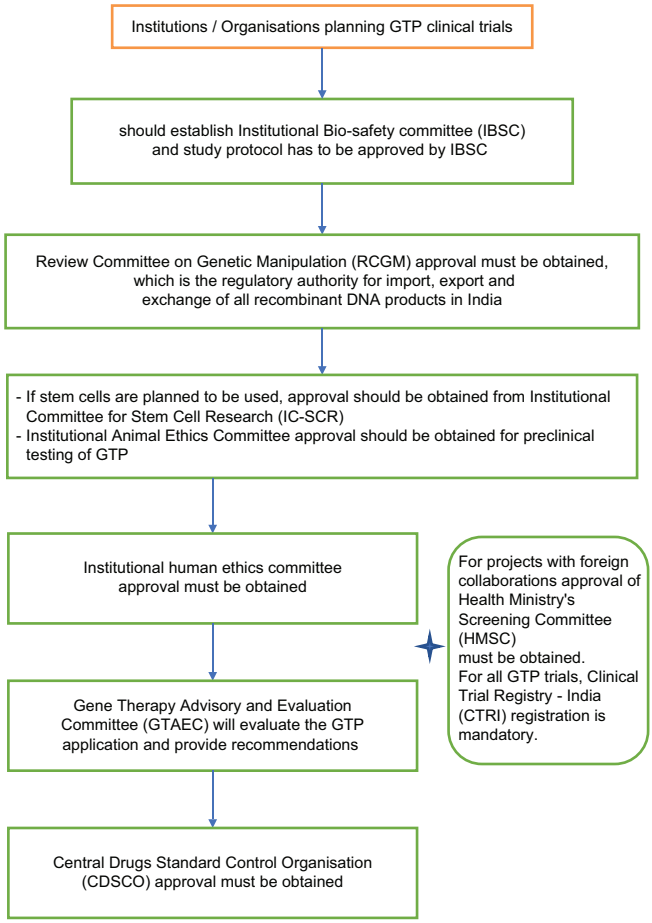

Figure 1: Flowchart of review process for gene therapy product clinical trials protocol

professionals with good clinical practice certification. All stakeholders, including investigators, institutions, and sponsors, bear ethical and legal responsibility of conducting the research activities according to the approved protocol fulfilling the national regulations and guidelines. If the GTP trial involves the use of stem cells, then it must be conducted in compliance with the national guidelines on stem cell research.[14,15] All the human biological material needed for GTP clinical trial should be obtained from institutes and hospitals affiliated with the ethics committee. Adequate unbiased information about the GTP trial should be provided to the participants, and no unrealistic expectation in participation should not be given.[16] The institution involved in GTP trials must maintain the pertaining records for a period of 15 years. The anticipated risk and benefits of GTP clinical trials must be explained to the participants and details about the same must be incorporated in the consent forms.

International collaborative projects need to get approval from the respective funding agencies followed by which approval from Health Ministry's Screening Committee needs to be obtained.[17] Permission from Review Committee on Genetic Manipulation, GTAEC and CDSCO is required for the import of GTP or any of its components. The imported GTP must undergo preclinical animal studies if it is planned for direct first in human trials in India. On the other hand, if the imported GTP already has well-established clinical safety and efficacy in humans, then clinical trials in humans in India are allowed depending on the target genetic disease with prior approval from GTAEC, CDSCO, and Cellular Biology Based Therapeutic Drug Evaluation Committee. In case, a scientific or ethical conflict is arising among the collaborators, then the current Indian guidelines have to be implemented for research work on GTP which is planned to be taken up in India.

GUIDING PRINCIPLES FOR THE CHEMISTRY, MANUFACTURING AND CONTROL AND QUALITY ASSURANCE OF GENE THERAPY PRODUCTS

The information regarding chemistry, manufacturing, and control (CMC) requirements and procedures followed during production process (i.e., development, manufacturing, and testing) of new GTP must be submitted to the regulatory authority along with the GTP clinical trial application. The priority put forth to the manufacturers is the selection of a production unit with good manufacturing practice (GMP) and good laboratory practice (GLP) certified facilities.[18,19] Some salient features which should be considered about the CMC requirements for GTP are enlisted in Table 3.

Gene therapy products banking

Master cell/gene therapy products bank

Information regarding the source, methods of production, stability, and characteristics of Master cell bank (MCB) stocks such as cell numbers, density, unique identification numbers must be enclosed under CMC requirements of GTP. Adequate and appropriate testing of MCB must be performed and documented to ensure the absence of pathogens such as cytomegalovirus, human immunodeficiency virus (1 and 2), human T-cell leukemia virus (1 and 2), Epstein–Barr virus, hepatitis B virus, and hepatitis C virus.

Working cell/gene therapy products bank

The source of working cell bank (WCB) might be obtained from the multiple vials of MCB stock and these WCB must be tested for the following:

- *In vitro* adventitious viral agent testing
- Replication competent virus testing
- Bacterial and fungal sterility
- Mycoplasma testing
- Limited identity testing (e.g., Southern blot and flow cytometry).

The testing of MCB and WCB must be carried out in compliance with ICH Q5D guidelines:[20]

Final gene therapy products

Figure 2 highlights the salient points which have to be provided about the final GTP under CMC requirements of GTP clinical trial application.

TRANSLATION OF GENE THERAPY PRODUCTS TO NEW DRUG

Preclinical trial requirements of gene therapy products

The animal model selected for preclinical evaluation of GTP should be homologous in genotype or phenotype to the target genetic disease. Route of administration selected for GTP administration must be target site specific and the least invasive route with low risk of immunogenicity. For determining pharmacokinetics parameters and dose range, dose escalation model would be appropriate. The off-target effects and toxicity of GTP can be monitored through multiple end-point assessments. In case, the investigational GTP is intended to be used in the pediatric population, age-dependent dose-escalation, and safety studies are required. It is mandatory to run a screening test for environmental risk assessment to check for the GTP getting discarded in the body fluids of test animals. It is also advisable to perform other additional tests depending on the different components of the GTP like rodent carcinogenicity test for assessing long-term safety of a component which is known for its oncogenic potential.[21]

Clinical trial requirements of gene therapy products

Disease information

For all GTP, the molecular function of the gene of interest must be described in the context of the target genetic disease. In addition, the natural history of the disease, genotype to phenotype correlations, and clinical sequelae

Table 3: Some salient features of the chemistry, manufacturing, and control requirements for various components of gene therapy products

Vector component	Cellular components	Other components
Information regarding the following components should be provided Vector sequence: Molecular structure, detailed genetic sequence analysis, and its regulatory elements If a viral vector is used, its biophysical and biochemical characteristics, helper plasmid and viral capsid must be provided If bacterial vector is used, details about its physical, biochemical properties, growth characteristics, genetic markers, and regulatory elements must be mentioned	For autologous as well as allogenic cells, the following details should be mentioned Cell source Methods used for mobilization, activation expansion, collection and recovery of stem cells For genetically modified cells, information on the gene editing technology used should be mentioned	Reagents These are components which are used in the process of manufacturing GTP and might influence the performance of GTP They are not retained in the final product Details about its concentration, source, grade and manufacturing step at which it is used must be provided Excipients These components such as serum albumin or dimethyl sulfoxide are included in the final product Details about its concentration, source, and specifications must be provided

GTP=Gene therapy products

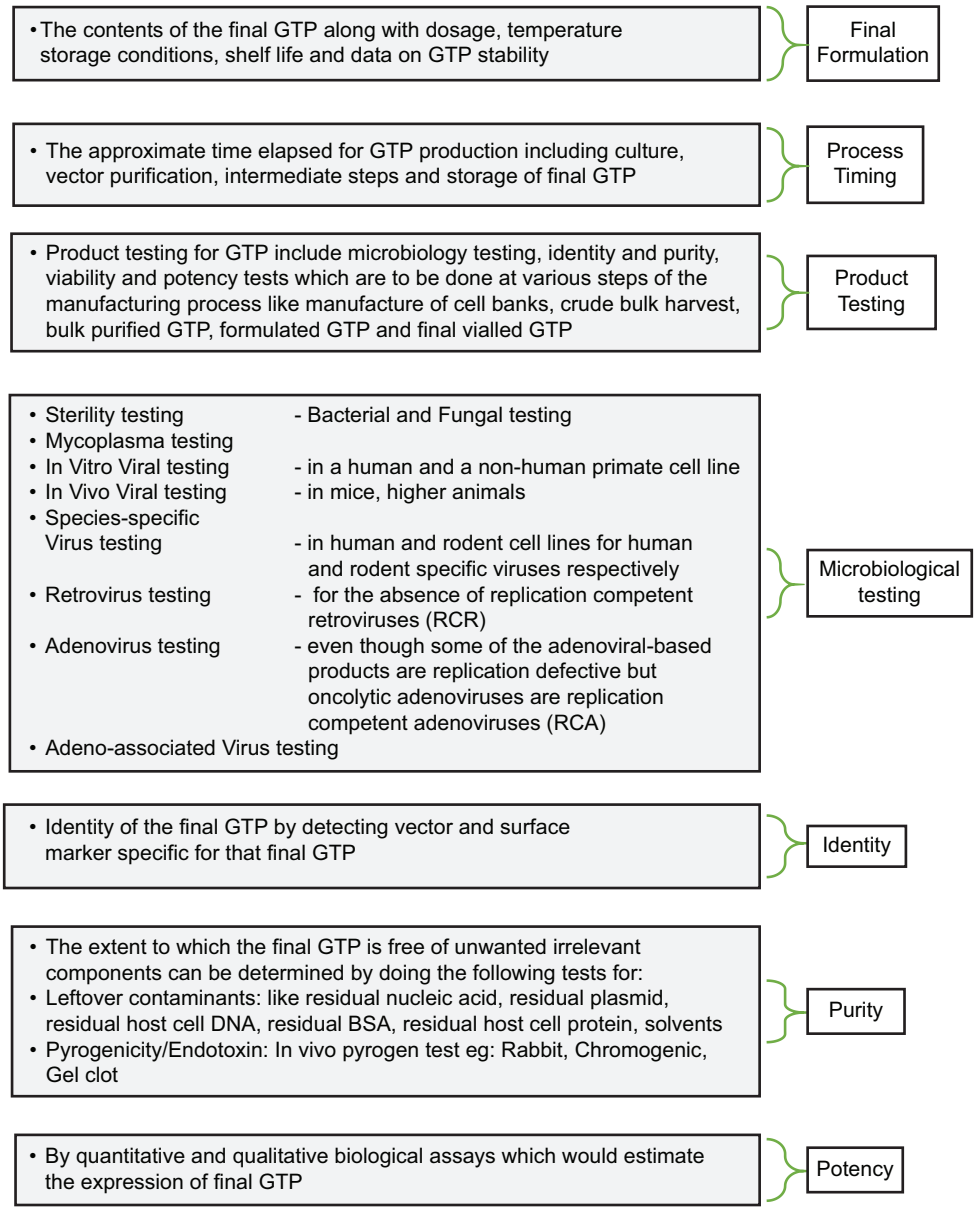

Figure 2: Information to be furnished on final gene therapy product

need to be considered when designing GTP trials. If the data regarding natural history of the disease is lacking for subjects to be recruited in GTP trials, then historical comparators such as prior data, published natural history studies, and established clinical markers of milestones can be used for selecting subjects.[22]

Patient selection for gene therapy products trial

The clinical phenotype of the target genetic disease must be clearly described and further substantiated by various imaging, biochemical, structural, or morphological data. To define the inheritance pattern, sequencing validation must be tested among family members. Information on clinical severity and staging of the target disease, presence of co-morbid medical conditions must be obtained. Since they might influence the clinical efficacy and selection of route of administration of GTP, the level of preexisting antibodies or T-cell response to the GTP vector or gene product must be established for potential trial subjects to reduce adverse immune reactions mediated by them. Details about the previous and ongoing immunosuppressive therapies (allopathy or alternative medicine) to which the subjects have been exposed must be mentioned. As the risk involved in GTP trials is high, healthy volunteers and placebo group should not be included.

Study design

Usually in GTP trials, the number of patients who fulfil the eligibility criteria for enrolment tend to be less,

leading on to small sample size. Hence, it is advised to stratify the patient population based on disease severity, comorbidities, and genetic information. Sometimes, due to ethical issues, clinical reasons, and surgical complexity of the route of administration, blinding may not be feasible in GTP trials.

Gene therapy products dose selection and administration

GTP dose selection should be done based on the data obtained from preclinical studies or from the study results published based on the trials carried out in other countries with similar GTP. In case of first in human use GTP, the participants must be hospitalized at least 24–48 h before infusing GTP. The process of GTP administration must be performed in an operation theatre. After completing the procedure, the patients must be hospitalized and closely monitored for the next 48–96 h. Postadministration of GTP, immune reactions might occur against the vector and other components. The route of administration of GTP and stage of the disease might also trigger these reactions. Hence, it is advisable to implement transient immunosuppression, and the details about the immunosuppressants used must be mentioned.

Patient withdrawal criteria

Prior to GTP administration, subjects recruited can withdraw from trial at any point of time without prejudice to their ongoing treatment. However, after GTP being administered to the patient, it is advised not to withdraw from the study and they should be followed up in order to evaluate long-term risks and benefits to the patient.

Gene therapy products trial endpoint assessment

The endpoints planned must be multifaceted to evaluate safety, efficacy, clinical and disease specific parameters of the target genetic disease. Some of the important endpoints which must be included in GTP trial are elucidated below:

Safety endpoints

All adverse events and serious adverse events must be immediately informed to the ethics committee and CDSCO. The immunological endpoints which must be closely monitored after GTP infusion are the following:

- Off target organ toxicities (neurotoxicity, hepatotoxicity, and myotoxicity)
- Occurrence of cytokine release syndrome.

Efficacy endpoints

The therapeutic endpoints for GTP trials must include assessment of the following parameters:

- For observing the effects of GTP on the host (bioactivity of the GTP)
- Biochemical, enzymatic, sequencing-based endpoints for evaluating gene transfer
- Functional improvement in disease-specific parameters.

If there is lack of well-established efficacy endpoints then surrogate efficacy endpoints can be included.

Patient experience assessment

The most important goal of gene therapy is to improve quality of life (QoL) of the patient. Hence, strategies such as questionnaires and QoL measurements must be included in GTP trial at various time points (pre- and post-GTP administration) to evaluate the patient experience parameters.

Follow-up time period

The follow-up time period might vary for different genetic diseases depending on the natural history of disease and several other factors. Ideally, it is recommended to follow-up the patients for a period of at least 5 years post-GTP administration and for 10 years post marketing. Same GTP can be re-administered to the patient only after a period of 1–2 years, provided there is the absence of adverse immune reactions during this period.

CONCLUSION

Gene therapy is a promising field of biomedical research and improving the safety and efficacy of gene therapy is the need of the hour. The United States and Europe are the pioneers in this field with clinical trials being carried out for more than two decades and India has stepped into it with much more awaiting results. Recently, here has been a surge in the number of gene therapy research activities in India. Ethical issues observed in the past related with the use of gene therapy technologies led to the development of stringent guidelines and regulations to avoid its misuse and premature commercialization. Hence, it is the responsibility of all the stakeholders to develop the strategies for adhering to the national guidelines to make gene therapy a reliable treatment option in future. These guidelines and regulations are dynamic and will have to be looked upon from time to time as per the changing global standards. Elaboration of strategies based on specific genetic diseases will also be a welcoming adds on to the update of the current guidelines.

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Conflicts of interest

There are no conflicts of interest.

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