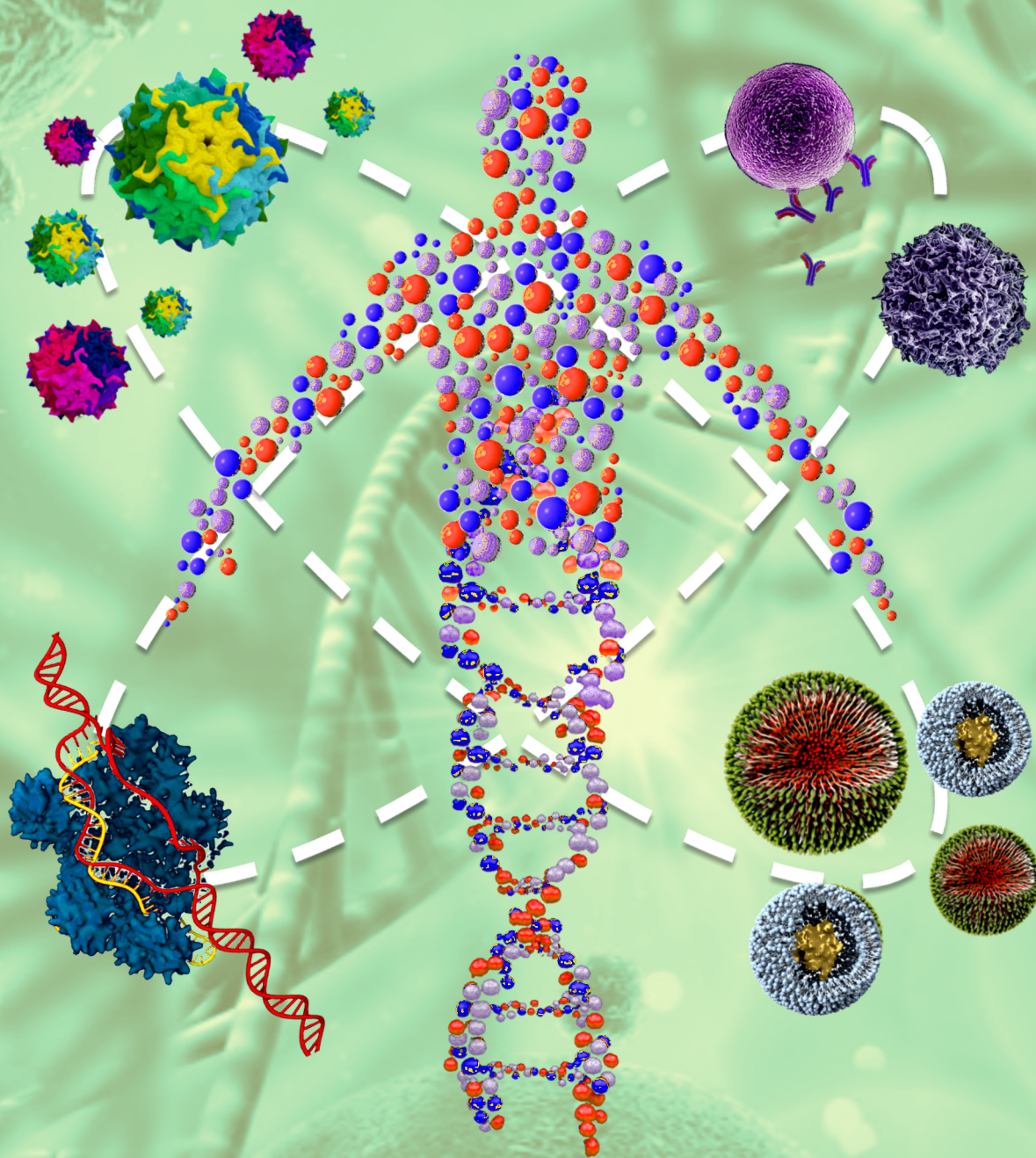


National Guidelines for Gene Therapy Product Development and Clinical Trials



Central Drugs Standard Control Organization
Ministry of Health & Family Welfare
Government of India



सत्यमेव जयते

Department of Biotechnology
Ministry of Science & Technology
Government of India



Indian Council of Medical Research
Ministry of Health & Family Welfare
Government of India

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Indian Council of Medical Research
Department of Health Research



Central Drug Standards Control Organisation
Directorate General of Health Services

Ministry of Health & Family Welfare
Government of India
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FOREWORD

The field of biomedicine is constantly evolving with new discoveries. The discovery of genes, gene expression mechanisms, genetic mutations and protein function in the middle of last century were the turning points bringing us closer to understanding genes and their functions in normal and disease conditions. Further development of gene sequencing technologies, linkage and functional genetic studies provided unequivocal proof of disease pathology. Eventually, this paved the way for gene therapy wherein, scientists and clinicians around the world aspired to develop new strategies and techniques to target defective genes and restore normal functioning. Gene therapy encompasses different techniques facilitating the construction and delivery of genetic material that augments, alters or controls the inherent genetic defect causing disease pathology. Recent advances with development of robust technologies like genome editing, RNA, CAR-T and exon-skipping have also resulted in an increase in the potential applications of gene therapy.

Gene therapy gathered pace over the past couple of decades due to the rapid discovery of large numbers of genes which are mutated in a variety of diseases. Such diseases may be inherited diseases caused by single gene mutations or polygenic, complex disorders where many genes are mutated or their expression is affected. Gene therapy, can treat inherited diseases by providing a fully functional, “wild-type” copy of the gene which can recapitulate the functions required in the cell. However, in complex disorders such as cancers, gene therapy is often synthetic in strategy, wherein novel genes, such as suicide genes or tumor suppressors may be introduced into the tumor to selectively kill the cancer cells, or reprogram immune cells in the body to target the cancerous tissue.

Development of gene therapy products is a complex procedure involving a variety of chemical and physical means to transfer genetic materials into cells. Due to the natural ability of viruses to deliver genetic cargo efficiently into cells, viral vectors have emerged as the most favored gene transfer modality. Various molecular engineering strategies have been used to make the usage of viral vectors safe for humans to avoid adverse events. However, harnessing methods involving viral vectors often accompanies a variety of immune reactions which must be understood properly and carefully monitored in all such trials. Many of the early failures of human gene therapy trials in various diseases has provided us with important information

pertaining to patient safety, clinical trial design, production processes and quality required of the actual gene therapy product.

The complexity of human diseases and regulation of gene expression in cells has taught us to be cautious when designing strategies for gene therapies that alter the genome. To develop an ideal strategy to treat various diseases, it requires a great depth of scientific knowledge to design the gene therapy products for human applications. Worldwide, there are hundreds of gene therapies human trials being conducted by hospitals, Universities and industries, bringing hope to patients for whom no other form of treatment is available or successful.

India has large burden of genetic disorders and unmet medical needs and gene therapy can prove to be a turning point in treatment of such disorders. However, it also brings along with it unique technical risks and ethical challenges. Creation of babies using germline gene editing by a Chinese scientist recently, attracted global criticism and fuelled a debate on ethical concerns regarding applications of gene therapy technologies. This also brought to forefront the requirement of stringent guidelines and regulations to prevent misuse and premature commercialization. Many countries around the world have developed rules and guidelines to regulate gene therapy trials. Taking cognizance of situation, it was felt necessary to frame national guidelines and regulations to direct scientists and clinicians including industry regarding the procedures and requirements to be followed for performing gene therapy in India.

India stands at the cusp of a new era wherein the ideas of personalized treatment and precision medicine are expanding within both the clinical and patient communities. Therefore, the scientific, administrative and regulatory bodies of India have taken the lead and engaged collectively to generate the rules and guidelines for gene therapy products. Central Drugs Standard Control Organization (CDSCO) under Ministry of Health and Family Welfare recently notified New Drugs and Clinical Trials Rules, 2019 wherein gene therapy product is defined as ‘new drug’. Concomitantly, ICMR and DBT took initiative to frame the ***National Guidelines for Gene Therapy Product Development and Clinical Trials***. The US, FDA and EU guidelines were referred to while drafting this document. The guidelines were framed keeping in mind the existing rules and regulations. This document provides a broad framework on ethical, scientific and regulatory requirements for all those who aspire to test these advanced therapeutics; and do not address process specific and disease specific GTPs. These shall be drafted later in consultation with subject specific experts and added in due course.

It is also understood that the field is still nascent in the country and the scientists and industry involved need advice and directions regarding ethical, scientific and regulatory requirements for clinical translation of gene therapy products. ***Gene Therapy Advisory and Evaluation Committee (GTAEC)*** has been constituted and notified by Department of Health Research

(DHR), Ministry of Health and Family Welfare, Government of India as an independent body of experts representing diverse areas of biomedical research, concerned government agencies and other stakeholders. Amongst other functions this committee shall provide a hand holding for the investigators/ industry and also give pre-IND consultations.

We hope that this document serves to clearly outline the ethical and scientific requirements for gene therapy trials, keeping in mind patient safety, efficacy and clinical rigor as cornerstone of this initiative. The aim of this document is to provide the basis of an enabling environment and guide scientifically sound practice that is ethical and beneficial to the patient. The document will be periodically updated on basis of scientific development in the field. These guidelines are not meant to be construed to replace or overrule other regulatory requirements.

To all those who refer this document, we implore that you to pay attention to details and work in compliance of these guidelines and we wish you the greatest success in your endeavors.



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Abbreviations

AAV	Adeno-associated virus
AE	Adverse Event
ASCI	Advertisement Standard Council of India
BSE	Bovine Spongiform Encephalopathy
CAR-M	Chimeric Antigen Receptor Macrophages
CAR-NK	Chimeric Antigen Receptor Natural Killer Cell
CAR-T	Chimeric Antigen Receptor T-Cell
CDSA	Clinical Development Services Agency
CDSCO	Central Drugs Standard Control Organization
CMC	Chemistry, Manufacturing and Control
CMV	Cytomegalovirus
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRS	Cytokine Release Syndrome
CTRI	Clinical Trials Registry- India
DBT	Department of Biotechnology
DCGI	Drug Controller General of India
DGHS	Directorate General of Health Services
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic Acid
DST	Department of Science and Technology
EBV	Epstein–Barr Virus
EOP	End of Process
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

GLP	Good Laboratory Practice
GTP	Gene Therapy Product
GTAEC	Gene Therapy Advisory and Evaluation Committee
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HMSC	Health Minister's Screening Committee
HSV	Herpes Simplex Virus
HTLV	Human T-cell Lymphotropic Virus
IBSC	Institutional Biosafety Committee
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research
IC-SCR	Institutional Committee for Stem Cell Research
EC	Ethics Committee
IND	Investigational New Drug
iPSCs	Induced Pluripotent Stem Cells
ITR	Inverted Terminal Repeat
MCB	Master Cell Bank
MCI	Medical Council of India
MOU	Memorandum of Understanding
MTA	Material Transfer Agreement
NIH	National Institutes of Health
OPDs	Out-Patient Departments
PCR	Polymerase chain reaction
PID	Primary Immunodeficiency
PMS	Post Marketing Studies

QC	Quality Control
QoL	Quality of life
RCA	Replication Competent Adenovirus
rcAAV	Replication-Competent Adeno-associated virus
RCGM	Review Committee on Genetic Manipulation
RCR	Replication Competent Retrovirus
RNA	Ribonucleic Acid
RoA	Route of Administration
miRNA	MicroRNAs
SAE	Severe Adverse Event
SEM	Scanning Electron Microscopy
(sh)RNA	Short Hairpin RNA
siRNA	Small interfering RNA
SOP	Standard Operating Procedure
TEM	Transmission Electron Microscopy
TSE	Transmissible Spongiform Encephalopathies
VERO	Verda Reno
WCB	Working Cell Bank

1. Preamble

Recent advances in innovative technologies have ushered a new era of cell and biological therapeutics. Amongst these, gene therapy is emerging as the potential treatment option for genetic disorders particularly for monogenic and rare diseases, as well as some of the multi-factorial diseases such as cancer. For some of these conditions, therapeutic strategies are yet to be established, but the genetic basis of the disease is understood, making gene therapy a modality of choice for clinical management. This is because these conditions result from gene defects or mutations and the reconstitution of a normal copy of the gene has the potential to mitigate the clinical phenotype. Furthermore, development of suitable vector systems, better clinical trial designs and monitoring, have made gene therapy a reality in the current scenario.

What encompasses gene therapy and gene therapeutic products (GTPs)?

Gene Therapy refers to the process of introduction, removal or change in content of an individual's genetic material with the goal of treating the disease and a possibility of achieving long term cure. It would include introduction and expression of an exogenous gene(s), chimeric or modifier sequences (DNA) to restore a missing/aberrant gene function or confer additional cellular properties. It also includes other gene therapy approaches such as: (a) expression of microRNA-adapted short-hairpin (sh)RNA, and small interfering RNA (siRNA) (b) gene editing by homologous recombination (with or without targeted DNA break) (c) clustered regularly interspaced short palindromic repeats (CRISPR) guided Cas9 (CRISPR associated protein 9) mediated gene editing or other similar gene modifying technologies. Thus, the term gene therapy encompasses all such processes wherein a nucleotide sequence (DNA or RNA) with or without its regulatory elements required for correction of a deleterious or defective genotype or phenotype is being introduced. It would also encompass such a process for improving the therapeutic efficacy of other gene therapy products. ***A gene therapy product (GTP) is thus defined as any entity which includes a nucleic acid component being delivered by various means for therapeutic benefit.***

The first successful gene therapy clinical trial was conducted in 1989 at the NIH Clinical Center, for severe combined immunodeficiency. Until 2017, almost 2600 gene therapy

clinical trials have been conducted worldwide in 38 countries, of which 64.9% were in USA, 23.2% in Europe and approximately 6.5% were in Asia. A comprehensive documentation of clinical trials involving gene therapy is available at www.genetherapynet.com. Within Asia, China has reported about 84 gene therapy clinical trials, followed by Japan (44 trials) and South Korea (14 trials). The vast majority of gene therapy trials have addressed cancer (66.6%), monogenic diseases (11.5%), cardiovascular diseases (6.2%) and infectious diseases (6.3%). The monogenic diseases include β -thalassemia, haemophilia A/B, sickle cell disease, Becker muscular dystrophy, Crigler-Najjar syndrome type 1 and retinal dystrophy due to RPE65 gene mutations. The commonly used vectors used for gene therapy trials are adenovirus (20.5%) followed by retroviruses (17.9%), naked/plasmid DNA (16.6%) and adeno-associated virus (7.6%). Majority of the gene therapy human trials performed are currently in phase I or I/II, with the two categories representing 77.7% of all gene therapy clinical trials.

Indian perspective of gene therapy: Every year millions of Indians are affected by inherited monogenic or complex diseases and have limited or no treatment options. A number of these genetic disorders are associated with life-long disability and are a significant economic burden to the society and the healthcare system. India has a large burden of monogenic diseases. These include haemophilia, thalassemia, sickle-cell anaemia certain forms of muscular dystrophies, retinitis pigmentosa, primary immunodeficiency (PID) in children, lysosomal storage disorders such as Pompe disease, Gaucher's disease, haemangioma, cystic fibrosis etc. In India, haemophilia A is reported in 11,586 patients although the prevalence is estimated to be around 50,000 patients. Similarly, there is a large burden of about 100,000 β thalassemia patients, around 150,000 sickle cell patients, 500,000 (Duchenne Muscular Dystrophy) for muscular dystrophy and a higher incidence of 1 in 4000 for retinal dystrophies. In addition, there is increasing recognition of the need to address rare genetic disorders prevalent in the community. Given the paucity of epidemiological data related to prevalence and burden of rare genetic disorders, the morbidity and mortality associated with them remains unknown. But, considering the international estimate of 6% to 8% of population being affected by rare diseases, approximately 72 to 96 million people in India can be expected to be affected by some form of rare disease, which is of major concern to the health care sector. So far, tertiary care hospitals in India have reported 450 rare diseases. India also has a huge burden of multifactorial diseases such

as cancer, with around 2.25 million patients affected by the disease and approximately, 7,84,821 succumbing to it every year. Therefore, it is imperative to establish safe, novel, targeted treatments for all such conditions in Indian patients. Making alterations to the genetic composition of an individual is a scientifically and medically challenging undertaking. If proper scientific and ethical procedures are followed, it can be a reality to alleviate patients' suffering. Since this nascent field is emerging in India, the Government of India (GoI) has proactively have come up with these guidelines to promote further research and streamline regulatory processes for future clinical trials using gene therapeutic products (GTPs). As per the New Drugs and Clinical trial Rules (2019) the GTPs falls under 'new drug' and shall always be deemed to be 'new drug'. Thus as per these rules 'academic trials' are not applicable to clinical trials using GTPs.

2. Aims and Scope

The aim of the document is to guide and enable the stakeholders to comprehend and comply with the regulatory requirements for research and development of GTPs in India. It also provides basic guidance for research involving human participants, including clinical trials, pertaining to the broad area of gene therapy covering all the technologies and processes for all mendelian, non-mendelian and other complex disorders. Disease-specific guidelines will subsequently be developed as part of standard operating procedures (SOPs) for different conditions. All GTPs being developed with the intention of potential human applications must adhere to these guidelines and should be used only under the purview of well-defined and approved clinical trials.

- 2.1.** The aim of this document is to ensure development of safe and effective GTPs, adhering to the following:
- a.** product quality characterization of the components and processes involved, the production process and quality control strategies for GTPs, clear chemical and biological definition of the final product;
 - b.** the pre-clinical evaluation of the GTP to establish, with reference to its dosage and route of administration, its safety profile, potency, bio-distribution, to identify the pharmacological/toxicological characteristics that support safety as well as efficacy of the GTP for human use;

- c. the clinical study design to establish safety and efficacy of GTPs in the target indication(s), GTP dosage(s), route of administration and selection procedures for patients and frequency of side effects or adverse events associated with any therapeutic strategy; and the process of regulatory approval for clinical trials.
 - d. Long-term patient follow-up to monitor its therapeutic benefit(s) and immune response or any adverse effect(s), if any, due to the GTPs.
- 2.2.** The term “GTP” is defined as a biologic (molecular therapeutic) that could introduce alterations in the genome, as mentioned in the preamble, including *ex vivo* gene modified/edited cells/tissues/organs, to achieve a therapeutic outcome. GTPs include substances that could introduce modifications of the genome in any form, modifications of extra-genomic (including mitochondrial and episomal) DNA/RNA segments and gene modified/edited cells/tissues/organs. The GTPs delivered using any means including but not limited to biological, chemical, physical or similar methods/processes will also fall under the purview of this guidelines. The GTPs include:
- 2.2.1.** *in vivo* and *ex vivo* molecular therapeutics such as:
 - 2.2.1.1.** Recombinant viral vectors (adenovirus, retrovirus, lentivirus, adeno-associated virus, herpes simplex virus, poxvirus etc.): recombinant viruses of various kinds which contain therapeutic gene of choice modified for reducing immune reactivity and gene delivery.
 - 2.2.1.2.** Non-viral vectors: naked DNA transfection, chemical (Polymer-based delivery, calcium phosphate etc.), biolistic (ultrasound mediated, electroporation etc), lipoplexes and polyplexes, exosomes and nanoparticle mediated.
 - 2.2.1.3.** Microbial/bacterial vectors (Salmonella, Listeria, *E. coli* etc.): recombinant bacteria derived vehicles that will deliver gene(s) of choice
 - 2.2.1.4.** Oncolytic viruses (vesicular stomatitis virus, herpes, reovirus, measles, adenovirus, vaccinia, etc.): these vectors will be delivered with the specific goal of killing the cancer cells that are being targeted
 - 2.2.1.5.** Modifications resulting from the use of CRISPR and other similar technologies would also be considered as GTP.
 - 2.2.1.6.** shRNA and siRNA, is included as a GTP

These components have been further elaborated in Section 8.2.

- 2.2.2.** *ex vivo* genetically modified cells: Cells (stem cells or other)/tissues/organs obtained from the human subject or suitable source modified using externally introduced gene elements for overexpression, removal of expression, correction or target gene editing for functional therapeutics or immuno-therapeutic outcomes. For example: gene modified/augmented stem cells, iPS cells, CAR-T cells, etc fall under the purview of GTPs.
- 2.2.3.** Soluble/particulate/emulsion/Nano based interventions containing any form of genetic material/nucleic acid for the purpose of clinical gene therapy will be also considered as GTP and fall under the purview of these guidelines.
- 2.2.4.** Combination of any of the above GTPs with other cellular/non-cellular drugs and/or devices for the purpose of treatment, augmentation or vaccination.
- 2.2.5.** Those DNA vaccines where the final product is nucleic acid and is administered for vaccination/therapy will fall under the purview of GTPs with additional requirements which will be specified subsequently.
- 2.2.6.** These guidelines prohibit germ line gene therapies as indicated in Section 4.1.
- 2.2.7.** Basic or exploratory research not involving human participants does not fall under the purview of these guidelines. They are required to follow pre-existing norms e.g. those related to bio-safety, animal ethics etc.

3. General Principles

Clinical trials on human participants involving GTPs must safeguard human rights, safety, dignity and fundamental freedom of the participant. This includes processes related to obtaining human tissues/cells for research, diagnosis and clinical trials. It is important that the fundamental tenets of beneficence, non-maleficence, justice and autonomy are adhered to. Research and clinical trials with GTPs must be conducted under specific requirements and guidelines described in this document. It is equally important to follow the general principles as laid down in the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017 (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf), which are highlighted below:

- Principle of Essentiality
- Principles of Voluntariness

- Principle of Non-exploitation
- Principle of Social Responsibility
- Principle of Ensuring Privacy and Confidentiality
- Principle of Risk Minimization
- Principle of Professional Competence
- Principle of Maximization of Benefit
- Principle of Institutional Arrangements
- Principle of Transparency and Accountability
- Principle of Totality of Responsibility
- Principle of Environmental Protection.

4. Classification of Gene Therapy

4.1. Germ-line gene therapy is applied to germline or gametes which can be transmitted vertically across generations. The concept of germ-line gene therapy is to introduce gene modified cells into the germline. However, germline or *in utero* gene therapy is prohibited in India, due to ethical and social considerations.

4.2. Somatic cell gene therapy is viewed as the only and more socially acceptable approach because it affects the targeted cells/tissue/organs in the patient, and is not passed on to subsequent generations. This also includes genome modification as exemplified by CRISPR-related and other technologies or epigenetic modulation by gene therapy approaches with similar effects. Somatic gene therapy has two categories: *ex vivo* and *in vivo*.

4.2.1. In the *ex vivo* approach, cells obtained from an individual are genetically modified/corrected outside the body followed by transplantation into the same or a different individual. In clinical trials involving *ex vivo* gene therapy, if the cells from the human participant (e.g. bone marrow, immune cells, stem cells etc.) are harvested and genetically modified (using recombinant viral vectors, e.g. CARs, gene editing, etc.) with or without expansion in the laboratory, the final modified cell is considered GTP. The vectors used in this process may integrate the gene of interest into the cell's genomic DNA or may remain as an episome, i.e. outside the genome. Thus *ex vivo* modified cells are

conferred new properties via the introduction of genetic material or modification of existing genes. For example, expression of novel chimeric antigen receptors on immune cells to target cancers (CARs), Stem cells expressing wild-type copies of mutated genes such as Factor IX, Factor VIII, Stem cells corrected for mutations using gene editing (CRISPR, TALEN, ZFN, etc) methods to now express a correct protein for disease such as haemophilia, muscular dystrophy, etc are all considered to be GTP and fall under the purview of this document.

- 4.2.2.** The *ex vivo* gene-modified cells are transplanted with or without expansion *in vitro*. Cells/Stem cells which are genetically modified through any technique involving the introduction of nucleic acid sequences to differentiate into organ-specific cell types to regenerate various organs such as brain, heart, lung, liver, pancreas, muscle tissues etc will also be considered GTPs. Introduction of *ex vivo* genetically manipulated stem cells shall require additional oversight and approvals as described in National Guidelines for Stem Cell Research 2017.

([https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines for stem cell research 2017.pdf](https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines%20for%20stem%20cell%20research%202017.pdf)).

- 4.2.3.** In the *in vivo* approach, the gene of interest is delivered directly to target cells/tissues/organs in the patients. Many tissues are potential targets for this approach. These include liver, pancreas, muscle, heart, skin, spleen, lung, brain, bone marrow, eye and others. Gene delivery can be carried out by viral or non-viral vector systems. Gene augmentation, replacement of a mutated copy of the gene by a healthy copy (via recombination), correction of mutation by gene editing (CRISPR, TALEN, ZFN, etc) methods, silencing of a dominant mutation (via shRNA or gene editing), altering the expression of genes by affecting transcription (transcription factors, epigenetic modulators) or splicing (exon skipping) are all considered to be GTP.

5. Scientific and Ethical Considerations in Gene Therapy:

Mutations, insertions, deletions and similar alterations in these genes or its regulatory elements may result in reduced or absent production of the encoded proteins, or expression of structurally or functionally abnormal proteins, thereby leading to genetic

disorders. GTPs work by repairing, replacing or deactivating dysfunctional disease-causing genes aiming to restore normal function. The biological and technical complexities of GTPs, their design and production pose challenges for their translation into clinic.

The scientific considerations for GTPs include selection of appropriate gene delivery vector/modality for the disease/tissue target, design of the expression cassette to ensure clinically relevant expression levels, specificity of gene expression to prevent unwanted side effects or off-target effects and minimising immune reactions of the host. The design of preclinical and clinical studies for GTP differ significantly from the other chemical and biological drugs, because of the complexity of the vector interaction with the host cells wherein the effects of vector uptake into host cells, response of the host immune system, the outcome of integration of genetic material into host chromosomes (in case of lentivirus or gamma-retrovirus) and levels of transgene expression from the host cells determine the final therapeutic efficiency of the GTP.

The GTP involves different components, such as the transgene cassette, the transgene regulatory systems, the delivery vectors and the cellular component (in case of ex vivo modifications). The scientific and ethical concerns for gene therapy primarily stem from the profound effect that genes exert on living cells by conferring novel properties and functions. The GTP ideally should not cause harm such as teratogenicity (e.g. integration of transgene cassette into tumour suppressor genes), excessive immune activation (e.g. aberrant CAR-T activity), introduction of unwanted mutations (e.g. off-target gene editing) or unwanted host immune response to GTP (e.g. neutralising antibodies to AAV). In addition, such gene augmentation techniques have the potential for misuse to gain unnatural advantages (e.g. in sports or defence sectors to enhance physical function) or to select for specific traits in new-borns (designer babies by gene editing). All such applications are prohibited unless scientific or ethical justification can be provided which is acceptable under socio-ethical norms and the laws of the land.

5.1. Vectors and gene delivery systems

Each gene therapy strategy involves the introduction of a functional nucleic acid (DNA or RNA) to target cells/tissues/organs. Nucleic acids are not spontaneously taken up by cells, thus special carriers (termed vectors) are required.

5.1.1. Vectors for gene delivery can be of either viral or non-viral origin. These vectors differ in accuracy, efficiency, and stability of gene expression. Viruses have evolved efficient mechanisms of transferring genetic information. Most of gene therapy experiments/trials have used recombinant viral vectors that are replication incompetent. The most commonly used viruses for gene therapy are adenovirus, retroviruses, adeno-associated virus, herpes simplex virus (HSV-1), vaccinia virus, baculovirus, etc. (<http://www.abedia.com/wiley/vectors.php>). Though viral vectors are very efficient in gene transfer and transgene expression, certain risk factors limit the efficacy of gene therapy, including cytotoxicity, immunogenicity, and insertional mutagenesis by integrating viral vectors and lack of site-specificity of transgene delivery. Recently, bacterial vectors have emerged as a promising tool to deliver very large DNA cargo such as chromosomes, but knowledge about their potential applications and pitfalls are still emerging. Non-viral vectors for gene therapy applications are being widely applied as well, primarily for targeted delivery. These non-viral methods such as naked DNA transfection using chemicals polymers or biolistic methods as well as nanoparticle, liposome, dendrimer, etc mediated delivery of nucleic acid sequences typically elicit less immune response. However, these vectors and gene transfer methods have lower efficacy than viral vectors. Therefore, the risk-benefit ratio for vector selection is critical when designing GTP applications. In addition, the clinical or surgical methods for delivering the GTPs must also be considered very carefully to ensure safety of the patient and success of the therapy.

5.1.2. Following advances have been made to overcome these hurdles:

- 5.1.2.1.** creation of extensively gene-deleted vectors that are less immunogenic; vectors which have reduced insertional mutagenesis potential; improvement of the GTP efficiency of the *ex vivo* transduction;
- 5.1.2.2.** increasing the tissue specificity, efficiency of *in vivo* gene transfer and transgene expression by using tissue-specific and/or inducible promoters;
- 5.1.2.3.** expanding the vector types for enhanced tropism and avoiding pre-existing immune response by developing alternative viral serotypes;
- 5.1.2.4.** the identification of new viral species or new materials/nanomaterials for vector development. In addition to recombinant viral vectors, conditionally

replicating viruses (Oncolytic virus) which show promise in tumour-directed gene therapy.

5.1.2.5. Non-viral vector systems which have applications for gene delivery include nano-particles or nano-compositions such as cationic lipids and cationic polymers that form condensed complexes (polyplexes, which use cationic polymers and lipoplexes that consist of cationic lipids) *via* electrostatic interactions with the negatively charged nucleic acid. Such vectors can be designed to incorporate carbohydrate or glycopeptide motifs for targeted receptor-mediated delivery to specific cell types *in vivo*.

5.1.2.6. Physical methods (electroporation etc.) and devices for gene delivery either alone or in combination with any of the above methods which can improve GTP application.

6. Mechanism for Review and Oversight

The field of gene therapy is associated with unique ethical, social and legal considerations for GTP usage that require additional oversight and expertise for efficient scientific and ethical evaluation. It is proposed to establish **Gene Therapy Advisory and Evaluation Committee (GTAEC)** with secretariat at Indian Council of Medical Research (ICMR) under the aegis of Department of Health Research (DHR), Ministry of Health and Family Welfare, Government of India. GTAEC shall be an independent body of experts representing diverse areas of biomedical research, concerned government agencies and other stakeholders. This committee will be composed of a core group of scientists and clinicians who have prior knowledge of gene therapy as evidenced by publications and participation in GTP clinical trials, as well as representation of the government agencies (ICMR, DGHS, CDSCO, DBT, DST, MCI). For each disease area in GTP trials, specific clinical consultants with extensive disease specific expertise will be co-opted to aid in the decision-making process (**Annexures I**).

The following mechanisms for approval and monitoring are proposed (**Annexure III**):

- 6.1.** The GTAEC will advise trial sponsors in designing and rigorously monitoring all first-in-human or existing GTP trials in India. GTAEC shall provide pre-IND consultation, if required by the applicants.

- 6.2.** It is mandatory for all institutions and entities engaged in development of GTPs to establish an Institutional Bio-safety committee (IBSC), constituted as per the Regulations and Guidelines on Bio-safety of recombinant DNA Research and Bio-containment 2017. All bio-safety related procedures should be in compliance with these guidelines.
- 6.3.** Research involving development of new GTPs needs to obtain approvals from IBSC and Ethics Committee (EC). In the event the GTPs involving stem cells are proposed, additional approval from the Institutional Committee for Stem Cell Research (IC-SCR) is required.
- 6.4.** GTPs should have prior approval of Review Committee on Genetic Manipulation (RCGM).
- 6.5.** All clinical trial applications using GTPs should be evaluated and recommended by GTAEC prior its submission to Central Drugs Standard Control Organisation (CDSCO).
- 6.6.** Approvals from EC of the participating sites/institutions are mandatory before initiating the clinical trial.
- 6.7.** All clinical trials are mandated to be registered with CTRI.

7. Responsibilities of investigators/institution/sponsors/EC/committees

As detailed in Section 6, GTPs have unique scientific and ethical concerns. Hence its use needs a rational study design and rigorous oversight. Regular review of progress in this field ensures the highest degree of scientific rigor and resolution of ethical concerns. Members of the IBSC and EC shall regularly update themselves with regard to advances in the field and existing guidelines and relevant rules. Given below is a summary of their responsibilities:

- 7.1.** It is mandatory for all investigators, institutions and sponsors conducting or involved with research, development and clinical trial to fully understand and be conversant with this document. The investigators and institutions involved in research, development and clinical trial bear the ethical and legal responsibilities of ensuring that research activities are in accordance with approved protocol and in compliance with the existing national regulations and guidelines.
- 7.2.** The investigator/sponsor shall endeavour to avoid any activity that leads to hype, or unrealistic expectations in the minds of study participants or general public regarding the status of Gene therapy in general, or specific to their R & D activities.

- 7.3. Biological material from humans can be procured only from clinics/hospitals that have an EC. The EC must ensure that the SOPs are in compliance with the national guidelines. Investigators should treat the biological material with utmost respect and adequate care to avoid its misuse.
- 7.4. The institute needs to define SOPs for development, production; storage and disposal of the GTPs or its components should be as per the Regulations and Guidelines on Bio-safety of Recombinant DNA Research and Bio-containment 2017. The institute needs to perform appropriate risk assessment to ensure containment measures are in place prior to safe operation to ensure product/personnel protection.
- 7.5. The GTPs used in the clinical trial should be manufactured in GMP facility after obtaining appropriate licence from concerned regulatory authority. The GTPs should be processed in an approved GLP and GMP facility (Drugs and Cosmetic Act, 1940 and Rules therein).
- 7.6. If the GTP manufacturing is out-sourced, the investigator should obtain product specific GMP compliance (schedule M of Drugs and Cosmetic Act 1940) document from the manufacturer.
- 7.7. Exchange of indigenously developed GTPs or its components with investigators/institutions within the country or outside the country must be done with prior approval of EC and IBSC with appropriate MoUs or MTAs (material transfer agreement) on record.
- 7.8. As per the Rules 1989, RCGM is the authorized regulatory authority for import/export and exchange of all recombinant DNA products in the country. RCGM approval to be submitted along with the dossier to GTAEC and CDSCO for clinical trial approval.
- 7.9. Any GTP of foreign origin or its modified variants that will be first in human use is not permissible for direct first in human trials in India.
- 7.10. Imported GTPs or its modified variants must undergo preclinical animal model studies with due approval of RCGM followed by GTAEC and CDSCO to apply for first in human trials in India.
- 7.11. It is mandatory to have prior approval of HMSC with information to GTAEC, for international collaborative projects/global clinical trials.
- 7.12. The study participant and/or legal representative should be provided with adequate

and unbiased information about the trial protocol, its limitations and potential adverse effects.

- 7.13.** Investigators should demonstrate respect for autonomy and privacy of patients undergoing gene therapy trial and procure all necessary and appropriate consents prior to enrolment in the trial. It is the responsibility of the investigator to generate robust scientific evidence through well designed clinical trials that could yield valuable information for the benefit of patients. The clinical trial must have a medical specialist registered with the MCI and holding a MCI approved post graduate qualification in the subject domain of the trial.
- 7.14.** Clinical trials can only be conducted in accordance with New Drugs and Clinical Trials Rules, 2019.
- 7.15.** Clinical trial using GTPs should only be conducted in a medical institution/hospital with adequate infrastructure with tertiary care facilities
- 7.16.** All medical professionals involved in clinical trials should have a valid GCP/ICH certification obtained from agencies such as Clinical Development Service Agency (CDSA) or through online courses conducted by National Institutes of Health (NIH) USA.
- 7.17.** All records pertaining to GTPs and clinical trials must be maintained for a period of at least 15 years. The head of the institution should facilitate the maintenance of records through investigator(s). Participants enrolled for clinical trials are not liable to pay any charges towards procedures, investigations and/or hospitalisation related to the trial. However, PMS studies can be charged on a case to case basis as per decision of the CDSCO.
- 7.18.** Institutions conducting development of GTPs or/and gene therapy clinical trials involving stem cells shall work in compliance with National Guidelines for Stem Cell Research (NGSCR) -2017, wherever stem cells are involved.
- 7.19.** Clinical Trial sponsors shall take note of their responsibilities and liabilities under various statutes, regulations and guidelines governing research and development in this field in India.
- 7.20.** Government agencies/ other sponsors facilitating or supporting gene therapy trials must ensure that the projects submitted for financial support has prior approval of GTAEC and CDSCO. The research and development of GTPs through preclinical animal studies require prior approval of IBSC and RCGM.

- 7.21.** For multi-centric clinical trials, all participating sites should obtain approvals from their respective individual EC.
- 7.22.** Each institution shall have an empanelled roster of investigators conducting gene therapy trials and ensure that national guidelines, regulations and best practices are followed.
- 7.23.** Institutions conducting gene therapy trials shall establish suitable mechanism for creating awareness amongst the scientific community and the public at large.

8. Considerations for Chemistry, Manufacturing and Control, Quality Assurance, Product Attributes for Human Gene Therapy Products

This document governs the use of human GTPs and combination products that contain a human GTP in combination with other devices or drugs. Since the field of gene therapy is emerging in the country, this document has been developed and has been harmonized with all existing rules and regulations and should be followed at every stage of GTP development/ administration, as applicable. In addition to the Chemistry, Manufacturing and Control (CMC) information, the requirements as defined in Drug and Cosmetics act, 1940 and rules therein, are applicable in assessing GTP specifications and release criteria testing.

This section is intended to provide requirements for CMC of GTPs for human use. These must be implemented by the manufacturer for the production of GTPs and needs to be submitted for regulatory approvals. The purpose here is to guide regarding requirements to assure product quality in terms of purity, safety, identity and strength (concentration and/or potency).

8.1. Product Manufacturing (GMP-grade) – Components and Materials

As elaborated in Section 2, GTP is a combination of two or more of the following components:

- a.** Gene of interest and its regulatory sequences: Gene of interest is defined as the therapeutic gene, or gene regulatory sequence, chimeric gene, gene editing sequences, etc. The regulatory sequences would be promoters, polyA, regulatory factor binding sequences, etc. The gene of interest is the primary source of the therapeutic effect.

- b. Vector or gene transfer vehicle: The delivery system for the gene of interest is called the vector or transfer vehicle. The vector may be of viral, non-viral nanoparticle, liposome, chemicals or polymer in origin. The primary function of the vector is to ensure the efficient transfer of the cargo gene of interest to the correct target tissue.
- c. Cellular component wherever applicable (stem cells, CART-T cells, tissue etc): This component includes all ex-vivo gene transfer modalities, such as correcting stem cells prior to implantation or generating CAR modified immune cells (CAR-T, CAR-NK, etc), enhancing/altering expression of tissue resident cells (for tissue or organ transplants). The modified cells/tissues will be considered as the complete GTP in these cases.

8.2. The Chemistry, Manufacturing and Control (CMC) requirements are provided to guide the development, manufacturing and subsequent testing of the new GTP.

8.2.1. The processes involved in producing GTP may evolve from the development stages to the batch production and manufacturing stages and such amendments to the process protocols must be properly documented. This information should be submitted for regulatory approvals.

8.2.2. If CMC information submitted during Phase-I studies, undergoes changes as the study proceeds, it is mandatory to inform any such changes to the regulatory authority before its implementation. Thus, all such changes must be documented prior to their implementation with adequate scientific justification and appropriate risk assessment to cover the changes made.

8.2.3. The information regarding the manufacture, storage and transportation of each individual component of the final GTP should be explicitly provided in an approved Product Specification File and should be in compliance with GMP.

8.2.4. The GTP should be defined and identified in its final active form in which it is to be administered.

8.2.5. Vector Components

CMC should include following details pertaining to vector component:

8.2.5.1. Vector Sequence and Maps: Information on the molecular structure,

including genetic sequence is mandatory. Genetic sequence should also be represented by submitting a schematic diagram that includes a map displaying all the relevant regulatory elements (e.g., promoter/enhancer, introns, poly (A) signal), restriction enzyme sites, and functional components (e.g., transgene, selection markers).

- 8.2.5.2.** Proposals involving viral vectors should include a description of the composition of the helper plasmids, viral capsid and envelope structures, as appropriate, and any modifications to these structures (e.g., modifications to antibody binding sites or tropism-changing elements) and their immunogenicity.
- 8.2.5.3.** The biophysical (e.g., molecular weight, particle size, SEM and/or TEM) and biochemical characteristics (e.g. glycosylation sites) should also be included in the GTP description.
- 8.2.5.4.** The nature of the genome of viral vectors, whether single-stranded, double-stranded, or self-complementary, DNA or RNA, and copy number of genomes per particle should also be mentioned.
- 8.2.5.5.** For bacterial vectors, physical and biochemical properties, growth characteristics, genetic markers (e.g., auxotrophic or attenuating mutations, antibiotic resistance) and the location (e.g., on plasmid, episome, or chromosome) and description of any inserted foreign genes and regulatory elements must be included.

8.2.6. Vector Sequence Analysis

- 8.2.6.1.** For vectors that are 40 kilobases (kb) or less, they should be sequenced fully, and an annotated sequence of the entire vector is submitted. For >40kb DNA in a vector, the sequence of active GTP component should be provided. In addition, restriction endonuclease digestion maps and their physical data should be included to describe the vectors in detail.
- 8.2.6.2.** Detailed sequence analysis should be performed on all GTP associated nucleic acid material, including their functional annotations, sequence characteristics such as promoters, open reading frames, introns, polyadenylation sequences, etc. including vector backbone components such as origin of replication and general features such as restriction sites,

etc. Details of the final GTP intended vector construction and cloning steps should be described.

- 8.2.6.3.** If the experimentally determined sequence of the gene is different from the expected sequence derived from available public resources or if certain changes are introduced into the genetic elements for improving GTP function, the significance of such sequence elements must be described and ascribed to functions, if any.
- 8.2.6.4.** Viral vectors should be sequenced from the master GTP (reference GTP, from which the working GTP stock is derived) stock or original product stock. The master GTP stock is well defined sample of the manufactured GTP which has all the genetic, sequencing, expression and quality control data well established to be used as a reference for quality and function.
- 8.2.6.5.** The sequences of GTPs developed using retroviral delivery systems should be accessed directly from the GTP stock (vector containing vials), the packaging cell line or from stably transduced cells (to verify integration, preferred integration sites, etc).
- 8.2.6.6.** The GTP and its production associated plasmid sequences must be obtained from verified sources. These should be of appropriate quality and suitable for downstream human application. The same should be verified independently by the applicant as part of the in-process quality check. All this information should be cited as such in the CMC document of application.

8.2.7. Cellular Components and Reagents for GTP Production

8.2.7.1. Autologous and/or Allogeneic Cells

The following information should be provided for both autologous and allogeneic cells:

- i. Cell source: The cellular or tissue of origin used for derivation/isolation of cells as well as donor details (demographic and clinical information) must be used to define the cell source. The donor screening to be carried out as per the guidance given in NGSCR 2017 guidelines.
- ii. Methods for mobilization/activation and expansion: All the treatment methods applied on the cells including, but not

restricted to, mobilisation of stem cells by GM-CSF, ligand activation of T-cells etc should be defined.

- iii. Procedures for collection, enrichment and recovery of cells should be established and validated clearly.

8.2.7.2. For *ex vivo* genetically modified cell GTPs, the expected major and minor cell populations being modified as well as the vector that contains the transgene cassette (transfer vector) that is transferred into the cells need to be identified. For introduction of reprogramming factors or novel proteins such as the chimeric antigen receptors (CAR), the vector and delivery vehicle (e.g. lentivirus) as well as the primary autologous cell source, method of identifying and selecting target cell types must be detailed and validated.

8.2.7.3. For cells that have been genetically modified using genome editing, the gene(s) that are altered and how the change(s) was made (i.e., the gene editing technology used) should be mentioned.

8.2.7.4. For cells of autologous origin, an assessment of the presence of pathogenic agents and the reactivity for specific pathogens should be made available.

8.2.7.5. Precautions to prevent the spread of viruses or other adventitious agents to persons other than the recipient should be described.

8.2.7.6. In an allogeneic setting, it is necessary to test for cells and tissues from donors for common blood borne pathogens.

8.2.8. Banking of GTPs

8.2.8.1. Master Cell/GTP Bank (MCB)/Packaging Cell Line information required:

Relevant details on the source, methods of obtaining and characterization of MCB (for vector production or for final therapeutic applications) in its entirety including final purity and safety aspects pertaining to adventitious agents testing are mandatory. All MCBs should be tested according to ICH Q5D guidelines and address the following:

8.2.8.2. The final MCB product characteristics, including its microbiological characterization and its stability.

8.2.8.3. Absence of common and specific pathogens such as CMV, HIV-1 & 2, HTLV-1 & 2, EBV, JCV, B19, HBV, HCV, etc as appropriate.

8.2.8.4. For cells/cell lines cultured in medium containing animal serum or other animal derived components, they should be tested for bovine and/or porcine infectious organisms. Such materials should be tested to ensure they are TSE/BSE free. If materials of bovine or porcine origin are to be used, they should be evaluated for compliance with the requirement for ingredients of animal origin used for production of biologics and sourced from reduced TSE/BSE risk countries.

8.2.8.5. Identity characterization of the cells, such as morphology, genotypes, biochemical and other relevant tests; their purity characterization; Testing for activity and maturation of cells according to the therapeutic nature of the cells at appropriate time points after generation and storage and a single time end-of production testing on MCB/packaging cells for genome stability.

8.2.8.6. Particulars of safety of banked products, such as:

- i. Documentation of all culture-related conditions used, details on methodology for vector exposure into the MCB, if any; characteristics of stocks of MCB (cell numbers, density and unique identification numbers etc.) The certificate of analysis of the individual component's, as applicable, should be provided.

8.2.9. Maintenance of GTP stock

A detailed description of GTP stock and all associated analytical data and testing procedures for ensuring safety, purity, and identity should be provided.

It is recommended that this section addresses the following:

8.2.9.1. History and derivation of the GTP stock

8.2.9.2. Detailed procedure followed for cell culture conditions and scale up.

8.2.9.3. Description and test results, if any, of the products such as media, media components, additives, cells, vectors etc used during GTP production.

8.2.9.4. Characterization of sterility, microbial components including contaminants- mycoplasma and adventitious viral agents including wild type virus (if the vector is recombinant).

8.2.9.5. The GTP stocks must be proven to be free of human pathogens or from pathogens of animal origin which may carry over into the final stocks from elements of the production materials and processes.

8.2.9.6. Data for testing of replication competent virus should be provided for the final GTP stocks.

8.2.9.7. Appropriate tests to establish identity of the GTPs such as sequencing southern blots, expression analysis of mRNA by quantitative PCR, northern blots, etc and protein product intended using western blots or staining of transduced cells/tissues.

8.2.9.8. GTP stocks must be stored under controlled and monitored conditions with clearly demarcated location and access/usage logs.

8.2.10. Working Cell/GTP Bank (WCB)

The WCB/GTP stock may have been derived from one or more vials of the MCB/GTP stock. If there is a two-tiered cell bank system in place (MCB, GTP stock), it is recommended that the WCB/GTP stock is tested for the following:

- i. *In vitro* adventitious viral agent testing;
- ii. Replication competent virus testing;
- iii. Bacterial and fungal sterility;
- iv. Mycoplasma testing;
- v. Limited identity testing (e.g., Southern blot, flow cytometry, capsid integrity).

8.2.11. Reagents

Reagents are components that are used for manufacturing GTPs but is not the final product. Given that they can impact the performance of GTP, it is suggested to provide the following:

- i. concentration of the reagent at the manufacturing step at which it is used; vendor/supplier; source of reagents (species of origin along with certificate of analysis) employed.
- ii. It is essential that clinical or cGMP grade reagents shall be used, as they are available. If a research grade material has to be used, information on source, safety of the reagent should be provided. If the vendor of the reagent has a regulatory file with the CDSCO, a cross-reference letter may be furnished.

8.2.12. Excipients

For the purpose of this guidance, an excipient is any component that is intended to be part of the final product, such as serum albumin or dimethyl sulfoxide

(DMSO). All excipients used during manufacture of the product that are intended to be present in the final product should be listed in the applications and preferably of pharmacopoeial origin. Concentration, source and information regarding specification of the excipients, shall be disclosed.

8.3. Product Manufacturing (GMP-grade) – Procedures

All procedures followed during production of the GTP should be provided. A flow diagram or schematic of the production and purification process and in-process and final product testing should be detailed more clearly.

8.3.1. Vector Production/Purification

It is recommended that information on the following is included: reagents/cells used for production, cell culture steps, processing steps, purification steps and storage information regarding all the components described above.

8.3.2. Preparation of Ex Vivo Gene-Modified Autologous or Allogeneic Cells

Cells (either autologous or allogeneic) can be modified by vectors. It is recommended that the following are detailed:

8.3.2.1. Method of Cell Collection/Processing/Culture Conditions

- i. A description of the cells that were modified *ex vivo*; e.g. immune cell sub-types used for expressing tumor targeting CARs such as CAR-T, CAR-M, CAR-NK, etc.
- ii. The processing procedures including number, volume and selection of cells, the protocol for their culture, and their final purity should be provided.

8.3.2.2. Ex Vivo Gene Modification

- i. A detailed description of the selection of cells, vector-based modification used such as, transfection, or transduction, should be provided.
- ii. If the cells are in culture after the genetic modification, information on the culture conditions used and time in culture should be mentioned alongside selection or enrichment criterion.

8.3.2.3. Irradiation of Ex Vivo Gene Modified Cells

- i. If the cells are irradiated, the desired cellular phenotypic and genotypic characteristics after irradiation should be included.

Details on calibration reports of the irradiator shall be included in this part.

8.3.2.4. Final Harvest

- i. A detailed description of the final harvest should be provided.
- ii. Whether the final GTP is centrifuged prior to final formulation, and if so, conditions of performing the washing and their reconstitution with media should be described. A description of storage conditions and the experimental data on the length of optimal storage should be included.

8.3.3. Process Timing and Intermediate Storage

8.3.3.1. An overview on the approximate time elapsed for GTP production including culture, vector purification, buffer/intermediate steps and storage of final GTP should be mentioned. These GTPs should be maintained in demonstrated aseptic conditions and its viability demonstrated.

8.3.3.2. However, if the final GTP is *ex vivo* genetically modified cells, the chain of custody from collection to storage should be explicitly provided.

8.3.4. Final Formulation

8.3.4.1. The final formulation of GTP, including excipients such as growth factors or human serum albumin as well as the source of these components should be mentioned.

8.3.4.2. The source and final concentration of these excipients used in the final product should be identified.

8.3.4.3. If the final product is delivered to a trial site, a description of shipping data (defined storage conditions such as temperature, relative humidity) and details on reconstitution of the GTP with consistent results should be mentioned. Any deviations should be addressed with a proper risk assessment and quality.

8.3.4.4. If the product is transported, data on GTP stability should also be included.

8.3.4.5. The container and the closure should be appropriate for the nature of vector and should not affect the quality of the final GTP.

- 8.3.4.6.** The shelf life of each GTP has to be indicated along with supporting stability data and rationale for determination.
- 8.3.4.7.** The investigators must provide periodic testing data for GTPs stored over time to establish loss of potency, degradation and toxicity. Appropriate methods such as *in vitro* testing, *in vivo* testing, gene expression analysis, or concentration/dosage changes must be used
- 8.3.4.8.** The contents of the final GTP along with dosage, temperature storage conditions, name of investigator/sponsor should be labelled explicitly on the primary label on the container and additional information provided in the secondary label affixed on the box containing the GTP. The containers used in a trial should also be labelled 'NOT FOR SALE AND FOR CLINICAL TRIAL ONLY'.
- 8.3.4.9.** Controlled/retention samples should be included for each batch of GTP and its validation performed, whenever appropriate. Sample batches may be requested by CDSCO for independent evaluation.

8.3.5. Product Testing

- 8.3.5.1.** It is recommended that product testing for GTP include, but not be limited to, microbiology testing, identity and purity, viability and potency tests.
- 8.3.5.2.** This testing should be performed throughout the manufacturing process, including on the manufacture of cell banks, crude bulk harvest, bulk purified GTP, formulated GTP and final vialled GTP to evaluate the manufacturing process itself and to ensure the quality and consistency of the product.
- 8.3.5.3.** Qualifications/specifications defined for acceptance and final product release criteria should be included.
- 8.3.5.4.** A tabulated form of test results pertaining to lot release, characterization testing and WCB/GTP stocks should be submitted.
- 8.3.5.5.** Deviations, if any, from established product testing norms should be disclosed.

8.3.6. Microbiological Testing

Microbiological testing should be performed on all cell banks, in-process intermediates, and the final product, as appropriate.

8.3.6.1. Sterility Testing (Bacterial and Fungal Testing)

- i. If antibiotics were used in manufacturing, documentation should be provided that the antibiotics were removed prior to sterility testing.
- ii. For some reason if the final product is not free from antibiotics, validity of the sterility assay should be assessed using appropriate detection methods.
- iii. If the GTP is an infectious agent, then appropriate risk assessment should be performed during GTP manufacturing and handling and must be included in the application documents.
- iv. It is recommended that in-process sterility testing is performed at critical points during manufacturing, such as during purification, or after *ex vivo* gene modification or extended culture periods.
- v. The timing /methods of sterility testing performed on GTP should be identified.
- vi. The test method chosen for in-process sterility testing should be adequate to provide assurance of product sterility.
- vii. If the final product is frozen before its use, it is recommended that testing is performed on the product prior to cryopreservation.
- viii. If the product undergoes manipulation (e.g., washing, culturing) after thawing, particularly if procedures are performed in an open system, sterility testing needs to be repeated.
- ix. The results of in-process sterility testing should be incorporated into the acceptance criteria for final product specifications.
- x. If the product has a short shelf life and must be administered to patients before sterility test results of the final product are available, then an alternate approach to provide sterility assurance will have to be identified. Certain GTPs like CAR-Ts may have to be infused almost immediately. In such cases, the release criteria may be based on 24-48 hr culture sterility tests and appropriate

molecular methods to ensure sterility and stability that may be conducted in consultation with GTAEC.

8.3.6.2. Mycoplasma

Several sources of mycoplasma contamination such as serum and cell culture facility environment exists.

- i. It is recommended that mycoplasma testing is performed on the product at the manufacturing stage when the test is most likely to detect contamination, such as crude bulk harvest, after pooling of cultures for harvest but prior to cell washing.
- ii. Testing shall be performed in both cells and supernatant.
- iii. During extended culture procedures, it is recommended to use of polymerase chain reaction (PCR)-based mycoplasma assays or other suitable rapid detection assay.

8.3.6.3. In Vitro Viral Testing

- i. When cell lines are used, the identity and protocol for *in vitro* viral testing performed must be described. Further, it is recommended to perform this testing on all stock/working formulations such as MCB, GTP stock, and final vector product, and as a one-time test on the EOP.
- ii. The choice of cells used for the viral testing (e.g. Hela or VERO) would depend on the species of origin of the GTP. However, it is recommended that a human and a non-human primate cell line could be potentially used with appropriate risk assessment measures.
- iii. Ideally, a monolayer culture from same species /tissue similar to the one used for generation of GTP, could be used for testing.
- iv. If the final product is a cytolytic virus, it will need to be neutralized by antibodies prior to adventitious testing of the GTP.

8.3.6.4. In Vivo Viral Testing

- i. *In vivo* viral assays should be carried out by inoculating the GTP into animals such as mice and the data submitted along with application.
- ii. It should be considered that testing on higher animals may be required if it is a first in human use GTP, on a case to case basis.

8.3.6.5. Species-specific Virus Testing

- i. The MCB and GTP stock should be assessed for species-specific virus and the protocol for the same, described.
- ii. If a human cell line is used for GTP manufacturing, human viruses (e.g. CMV, HBV and other blood borne viruses) should be checked while if rodent cell lines are used during product manufacturing the GTP should be tested for rodent specific viruses. The testing methods can be as appropriate including a PCR-based test system.

8.3.6.6. Retrovirus Testing

Retroviral-based products (including lentivirus and foamy virus-based products) used for most gene therapy applications are designed to be replication defective.

- i. To ensure the absence of replication competent retroviruses (RCR), testing for RCR should be performed at multiple points, during production of a retroviral vector.

8.3.6.7. Adenovirus Testing

The adenoviral-based products used for most gene therapy applications are designed to be replication defective, a notable exception being oncolytic adenoviruses. Replication competent adenoviruses (RCA) may be generated at a low frequency as a result of homologous recombination between viral vector sequences and viral sequences present in the cell substrate, during manufacturing. Therefore, for most adenoviral-based products, it is recommended the GTP stock be suitable for RCA and the production lot be tested for RCA.

8.3.6.8. Adeno-associated Virus Testing

Preparations of AAV vectors can be contaminated with helper virus-dependent rcAAV, also referred to as wild-type AAV or pseudo wild-type AAV. These rcAAV are generated through homologous or non-homologous recombination events between AAV elements present on the vector and AAV rep and cap sequences that are present, during manufacture. While wild-type AAV has no known associated pathology and cannot replicate without helper virus, expression of cap or rep genes in infected cells can result in unintended immune responses, which can

reduce effectiveness and may have unintended safety risks. Therefore, it is recommended that tests for rcAAV are conducted, which could potentially replicate in the presence of helper virus, and the results reported. A number of methods have been published for evaluating the level of rcAAV, including amplification of AAV in the presence of helper virus, followed by PCR for rep/inverted terminal repeats (ITR) junctions or PCR for rep and cap sequences, following DNase digestion of the vector preparation.

8.3.7. Final GTP

8.3.7.1. Identity

- i. The identity of the final GTP should be established and distinguished by tests from similar products generated in the same facility.
- ii. Testing should detect vector and possibly surface marker component of the final cellular product.

8.3.7.2. Purity

Product purity pertains to the ability of the finished product to be free from extraneous material, whether or not harmful to the recipient or deleterious to the product. This includes testing for pyrogenicity/endotoxin, residual proteins or reagents/components used for vector generation and *forex vivo* modified cells, a documentation of contaminating cells, if any.

i. **Leftover contaminants:**

- a. Quantitative testing of impurities and leftover contaminants such as residual nucleic acid, residual plasmid, residual host cell DNA, residual BSA, residual host cell protein, solvents etc should be performed on the crude GTP formulation as well as the final GTP.
- b. For a GTP which is an *ex vivo* gene modified cell therapy product (including gene edited cells, iPSCs, CAR-T, etc), appropriate purity testing should include a measurement of contaminating cell types. Details on purity testing methods should be disclosed.

ii. **Pyrogenicity/Endotoxin**

- a. The *in vivo* (e.g. Rabbit, Chromogenic, Gel clot) pyrogen test is preferred method for this purpose. Alternative methods if proposed should be detailed for their equivalence to established methods for pyrogen testing.

8.3.7.3. Potency

- i. All assays used to measure potency should be described and justified.
- ii. It is required that these assays are quantitative, in addition to a qualitative biological assay.
- iii. The test should measure the expression of GTP and it is recommended that a panel of *in vivo* or *in vitro* tests are used to quantify GTP biological activity.
- iv. All potency assays are a component of lot release and should be thoroughly validated prior to use of GTP.

9. GMP Guidelines: Infrastructure, Personnel

9.1. Organization and Personnel

- 9.1.1. Personnel Training:** All personnel engaged in GTP production for eventual clinical use must be well trained in aseptic procedures, testing for contaminants, GTP production processes (as per SOPs approved by IBSC) and maintaining all process related documentation. Qualification records should be available for gowning, cleaning, manufacturing process, final product filling and other critical operations.
- 9.1.2. Personnel qualification:** Such personnel must have scientific background and prior training in the field as evidenced from educational and training certificates (demonstrable qualification and experience) in an appropriate scientific field. The institute/entity engaged in GTP production must maintain training and health records of all such personnel with details of their roles.
- 9.1.3. Personnel responsibilities:** Personnel tasked with the manufacturing, associated processes, packing or handling of a GTP must wear clean, safe and appropriate clothing always in a GTP manufacturing facility and maintain aseptic conditions (SOPs for personnel entry and egress should be

maintained). Protective apparel covering the body, head, face, hand and arms, shall be worn as necessary to protect product from contamination (SOPs for the procedures must be maintained). Personnel must practice good sanitation and health habits. In addition, SOPs for entry of manufacturing components and disposal of waste components must be maintained.

- 9.1.4. Data entry:** All personnel must maintain documents/physical records of the work they perform with proof of aseptic conditions being maintained throughout the GTP manufacturing process, EOP and final product.
- 9.1.5. Personnel access:** The GTP production areas should be limited access with only authorized personnel being allowed entry. Only personnel authorized by designated supervisory personnel can enter the designated GTP production areas.
- 9.1.6. Quality Control Unit:** The quality control (QC) processes and procedures should be established to ensure the quality, purity, potency and identity of the final GTP stocks. The QC unit should approve of each batch of GTP produced by using proper tests to ensure that sterility and GMP are maintained at all critical processes and that all materials used are up to the stated standards. The final QC reports will be required for the approval of rejection of GTP batches.

9.2. Buildings and Facilities

- 9.2.1. Design and Construction:** Any building or facility used to manufacture, process or package GTPs should be of suitable size, location and constructed of appropriate clean room grade material to ensure proper cleaning, maintenance and production operations. Since production of GTPs (vectors, cells, etc) is a complex process which requires human intervention at all stages, special consideration may be given to the design of the GTP manufacturing facility to minimise process derived contaminating elements.
- 9.2.2. GTP manufacturing area:** GTPs should be manufactured in a Class A/Class B facility (as per Indian GMP guidelines). The bulk production of the GTP may be performed in either Class B or Class A facility but the final filling and packaging of the GTP must be performed in a Class A area. Materials and equipment used in such areas must minimise particulate matter (usage of clean room grade

steel, other materials, etc) and chances of biological or chemical contamination. Periodic aerobic and anaerobic microbial load should be monitored.

- 9.2.3.** *Air handling:* Air handling units must be appropriately equipped and validated for the area class with written documentation, testing and periodic maintenance. Air handling units for different class areas should be different with their own individual ducting.
- 9.2.4.** *Production area and monitoring:* The production and filling areas must be clearly demarcated and separated (SOPs of personnel and materials flow must be maintained). Appropriate particle counters, microbial sensors, air flow sensors, etc must be placed in the working areas of the GTP manufacturing facility and records maintained.
- 9.2.5.** *Area design:* Each designated work area in a GTP manufacturing facility must have appropriate space for the equipment, materials and personnel movement to prevent mix-ups between different components, in-process materials, or GTPs, thereby helping prevent contamination. If multi-product manufacturing facilities are used appropriate cross contamination studies need to be performed.
- 9.2.6.** *Instruments:* All instruments in the clean room areas for GTP manufacturing must have updated usage and calibration SOPs available with documentation of periodic maintenance.
- 9.2.7.** *Tissue and cell culture:* Cell culture during the production of GTP must be performed in appropriate biosafety cabinets with laminar flow by trained personnel.
- 9.2.8.** *Waste disposal:* Waste materials and by-products of the GTP manufacturing process must be securely decontaminated and transported as per appropriate biohazard disposal protocols (SOP should be approved by IBSC).
- 9.2.9.** *Process data:* Process SOPs must include methods for safety, prevention of contamination, periodic testing for contaminants, particulates and risk minimization. All data during the production process must be stored safely with limited supervised access and provided during evaluation process.
- 9.2.10.** *Facility validation:* The facility must be periodically validated for maintenance of air filters, instruments, etc confirming the maintenance of the designated Class area.

9.2.11. *GTP storage:* Postproduction GTP storage must be done in a limited access, physically secure area with access monitoring to the actual storage device (freezer, liquid nitrogen canister, etc).

9.2.12. *Sanitation:* Any manufacturing facility intended for production of GTPs for human use must maintain clean and sanitary conditions, without infestation by insects, rodents, birds, or other pests (excluding laboratory animals). Organic waste matter and other trash must always be disposed in a sanitary manner as per established SOPs. There should be written documentation of the procedures being followed with ascribed function to trained personnel which includes cleaning schedules, and material disposal.

9.3. Production and Process Controls

9.3.1. Written Procedures

The GTP production facility should maintain written protocols for production process control designed to assure appropriate quality, purity, concentration/strength and identity of the GTP. All such written procedures, and any amendments to them must be reviewed and approved by the IBSC and EC locally and by appropriate regulatory agency. These written SOPs and records should be submitted to the GTAEC and CDSCO when applying for a human trial. These SOPs must be followed carefully and documented during the entire production, packaging, quality checking and efficacy testing procedures.

9.3.2. Sampling and Maintenance of Materials

It is important to ensure batch uniformity and quality of GTPs, for which SOPs must be established and followed for each specific GTP type. These should describe all in-process quality controls being maintained or tested, examinations to be conducted at critical stages on samples of in-process materials collected during production of batch as relevant to the GTP. For certain GTPs, the GMP batch manufacturing may take several weeks or months, control of critical steps and intermediates during batch manufacture must be defined for storage at desired holding temperatures, holding time under appropriate product containment to ensure product quality and efficacy. The goal of these procedures would be to monitor the GTP output and evaluate the performance of the manufacturing process. Variability in GTP batches due to in-process variations must be documented for each GTP.

10. Requirements for Preclinical Evaluation of Investigational Strategies/Products for Gene Therapy

The pre-clinical evaluation of an investigational GTP is unique in scope and data assessment and depends largely on the target disease. Pre-clinical studies are warranted to test the rationale of GTP use and to subsequently predict the safety and therapeutic efficacy of the GTP, prior to its clinical application.

10.1. General considerations

Pre-clinical studies are a pivotal component in bridging the evolution of a GTP from a bench-side concept to the clinic. Therefore, the guiding factors for preclinical evaluation of a GTP shall include:

- i. a strong clinical and biological rationale for the use of GTP for potential intervention in a disease/condition
- ii. adequate feasibility assessment and development of an experimental approach specific to the target condition that will provide sufficient data on the risk/benefit profile of the investigational strategy or GTP
- iii. evaluation of delivery vehicles and (trans)genes or their products that primarily drive the on-target biological effects of the GTP mediating the phenotypic rescue
- iv. given the recent advancements in the field, to provide a basis for expedited pre-clinical evaluation of a GTP, on a case to case basis, if the GTP has been previously authorized for clinical use elsewhere for the same indication. This expedited pre-clinical evaluation is not applicable to GTPs that (a) are being developed for first clinical use, (b) is a modification of previously used GTP (c) warrant pre-clinical testing as a part of lot-release criteria of clinical grade GTP or (d) is based on previous outcome data only available from a “similar” GTP but not exactly the same GTP.

10.2. Requirements

The basic components of a pre-clinical evaluation shall include:

10.2.1. Selection of a suitable non-human model system appropriate for testing – *in vivo* and *in vitro* models

- 10.2.1.1. The use of animal models (natural mutant, transgenic or knock out versions of disease gene in relevant species) that are homologous in

genotype/phenotype to the ultimate clinical disease target, if available, is strongly encouraged. This would help in generating supporting evidence of the potential risk versus a clinical benefit directly relevant to the specific therapeutic nucleic acid (delivered as DNA, RNA or recombinant viral genome).

- 10.2.1.2.** The use of appropriate animal models also helps in documentation of secondary effects of GTPs such as its impact on any known or unknown related biological function, and genes and pathways involved in the phenotypic rescue.
- 10.2.1.3.** It is also important to demonstrate the delivery of the GTP agent to the target tissue and its effect on the expression of the gene of interest, or where relevant, down regulation of an endogenous gene expression.
- 10.2.1.4.** In the event that no specific *in vivo* disease models are available, the GTP can be evaluated by combination studies in suitable *in vitro* disease models and in normal strains of animals based on evidence in literature, on a case by case basis.
- 10.2.1.5.** For a GTP that is under pre-clinical evaluation for a first in clinical use, a tiered preclinical testing paradigm involving different assays for efficacy/toxicity documentation and both small and large animal models (if available) should be employed to characterize the functional attributes of the GTP.
- 10.2.1.6.** In the event, the GTP has been approved elsewhere for clinical use, it may be required to test only the clinical lot of vectors for outcome parameters as part of release criteria, unless there are variations in delivery vector, or transgene or in the production process of the GTP.

10.2.2. Efficacy testing: Primary objectives of preclinical testing with a stand-alone or multiple model system are demonstration of the feasibility of the proposed GTP for its potential application in a clinical condition by considering its efficacy and risks. Thus, a preclinical study should be ideally designed to study the following:

- 10.2.2.1. Vector and the nucleic acid cargo:** The choice of a specific mode and product for gene delivery (vector, transgene or RNA) should be guided

by antecedent evidence in literature wherever possible. Their administration should clearly demonstrate a biological response, i.e., alteration of pathways and/or specific forms of protein related to the target disease.

10.2.2.2. Route of administration (RoA): The RoA selected for GTP administration should reliably express the transgene product or deliver the functional RNA to the intended target site (Organ and specific cell type) during the preclinical testing. In case of multiple equally effective options, an RoA that is the least invasive and least likely to be immunogenic should be considered.

10.2.2.3. Pharmacokinetics, dose-response: Ideally, pre-clinical testing of a GTP should be performed in a dose escalation model. The initial studies should define the lowest minimally effective dose, based on the safety of the GTP and minimal outcomes, such as the confirmation of underlying scientific rationale of the study. Subsequent studies should optimize the doses for outcomes expected in the clinical trials, as well as the toxicity profile of the GTP delivery system. In addition, the pre-clinical dose-testing could also be used to assess the predictive value of end-point assays for efficacy and toxicity. If the GTP is a first of its kind developed either for preclinical or clinical use, further delineation of biologically active and relevant dose range should be done, wherever possible in multiple animal models, preferably including both small and large animals.

10.2.3. Safety testing and monitoring off-target effects, bio-distribution studies

10.2.3.1. Pre-clinical toxicological studies should facilitate the detection, quantification and/or resolution of acute and chronic toxicity of the GTP under investigation. Such testing protocols are expected to outline the acceptable risks of the GTP, while being efficacious enough when it is used through the same RoA, method of administration (MoA) and in equivalent dose (adjusted to body weight, if in vivo models are used) as in the intended clinical trial protocol.

10.2.3.2. Multiple administrations of GTP should be performed, if a similar schedule is expected in clinical trials.

- 10.2.3.3.** For toxicity testing, a disease model that mimics the pathophysiology of a human condition is preferred to studies in normal, immunocompetent animals.
- 10.2.3.4.** Multiple end-point assessments (both primary efficacy and safety endpoints) in the GTP administered models with adequate number of control groups are needed. Each such endpoint and the justification thereof for selection of the endpoints must be provided.
- 10.2.3.5.** A standard set of assessments to evaluate the biodistribution profile of GTP and its effect on systemic parameters with adequate follow up is expected to improve the overall safety data. For pre-clinical models, standard necropsy and testing of GTP presence in other organs should be tested and reported. Shedding of GTP vectors in secretions or excretions should also be considered.
- 10.2.3.6.** In case of a product that is being developed for first in use in the paediatric population, and if there is a chance of elevated risk for adverse events with the GTP, suitable age-dependent dose-escalation and safety studies will be needed.
- 10.2.3.7.** Additional lot to lot screening parameters such as the purity of the GTP, the presence of complete GTP (Vector + transgene) and presence of non-therapeutic proteins/biomolecules in the GTP formulation will help in minimizing the off-target consequences.

10.2.4. Environmental risk assessment

- 10.2.4.1.** A risk assessment screening to follow the shedding of GTP in the body fluids of test animals during its preclinical testing may be required, particularly if the GTP is for first clinical use.
- 10.2.4.2.** Safety assessment of revertant forms of vectors used as GTP (replication deficient to replication competent virus) may be considered to minimize biosafety concerns.

10.2.5. Conduct of additional studies

- 10.2.5.1.** As much as possible, manufacturing process for the proposed GTP to be used should be similar to that ultimately used in the clinical trial.

- 10.2.5.2.** If there are differences between the preclinical and clinical vectors, or their production process, evidence for their comparability in a single round of pre-clinical testing can be furnished and taken into active consideration by the regulators. In such cases, additional toxicity studies pertaining to clinical grade vectors may be required. Depending on the target disease and the organ involved e.g. Testis, the genotoxicity and the reproductive toxicity of the GTP may be warranted.
- 10.2.5.3.** In the event the GTP contains a transgene or a component that has known oncogenic potential, a rodent carcinogenicity test for its lifetime may be warranted to assess the long-term safety of the recombinant delivery vehicle.

11. Requirements for Clinical Trials

Diseases that arise from defined genetic alterations are often serious and bereft of proper therapies, thereby constituting a critical unmet need laying the foundation for clinical trials. The following section provides guidance for the clinical development and trial designs for investigational GTP intended for treatment of rare diseases (although they are not exclusively applicable to rare disease alone and does include complex diseases, cancers and transient conditions). For all GTPs, the molecular function of the gene must be described in the context of the disease. Additionally, the natural history of the disease, genotype to phenotype correlations and clinical sequelae need to be considered when designing trials.

- 11.1. Disease information and patient population for consideration in GTP trials:** This section details the molecular and clinical information required of the patients in order to consider them for GTP trials or therapeutic applications thereof.

- 11.1.1. Natural history of disease:**

- 11.1.1.1.** Inherited, familial disorders often have a well-defined genetic basis with mutation(s) in causative gene(s), typified by the clinical symptoms observed which must be documented in detail prior to considering patients for GTP therapy.
 - 11.1.1.2.** Despite having known genes being mutated, patients of monogenic, inherited disorders may still clinically present with broad heterogeneity

in disease severity and onset which must be taken into account during patient counselling and selection for GTP for therapy.

- 11.1.1.3.** The extent of tissue damage which led to a disease may be critical to the success of the therapies, therefore establishing the natural history of the disease along with relevant structural information (imaging, MRI, OCT, etc) is critical prior to planning GTP treatments and determining the effectiveness and safety of the therapy.
- 11.1.1.4.** In the absence of sufficient information regarding natural history of the disease for subjects to be enrolled in GTP trials, historical comparators (prior data, published natural history studies, established clinical markers of milestones, etc) would be required for selection of subjects, their disease staging and clinical endpoints in trial design.
- 11.1.1.5.** While the genetic basis of complex, multi factorial disorders including cancers typically are defined only in a small subset of patients, the clinical symptoms across a wide variety of patients may remain similar. Therefore, detailed clinical categorisation of the associated symptoms, disease specific pathological features and clinical endophenotyping in conjunction with associated co-morbid pathologies is necessary to establish the clinical parameters for cancer/complex disease trial design, patient recruitment, endpoint determination and risk estimation.
- 11.1.1.6.** For complex diseases, the natural history of the disease must be taken into context when selecting the suitable GTP – CAR-T, CRISPR, gene augmentation or others.
- 11.1.1.7.** A large proportion of the genetic disorders manifest in early life, therefore entailing important ethical, clinical and regulatory considerations for trial design. The appropriate window for treatment may be early in the disease process in certain cases and hence both natural history and historical comparator evidence must be provided by the trial sponsors for patient enrolment. These factors must be factored into the trial design and execution in early and late phases.
- 11.1.1.8.** During trial design, the clinical team needs to consider the expected outcomes relative to the natural, clinical history and expected disease progression in the subjects to be enrolled.

11.1.2. Patient selection for GTP trial (inclusion/exclusion criteria)

Selection of patients for a GTP trial must be given thorough consideration. The sponsors must define the detailed subject selection criteria from within the affected population to establish if the trial design is likely to provide informative safety and/or efficacy data. The potential benefits of the therapy must be established thoroughly on the basis of the pre-clinical data, historical evidence from other trials and natural history of the disease in the affected population. The following points should be considered with respect to trials of GTP:

- 11.1.2.1.** The primary criterion for inclusion of subjects in a trial is a clear, well described clinical phenotype of the disease supported by various imaging, biochemical, structural or morphological evidence.
- 11.1.2.2.** For first in human trials, patients without clear clinical diagnosis or with multiple overlapping conditions (unrelated to the therapeutic application) must be excluded.
- 11.1.2.3.** Inclusion of patients with end stage disease must be clearly justified scientifically and clinically with proper determinants of efficacy.
- 11.1.2.4.** The clinical trials using GTP are mostly single-arm trials and therefore historical data and natural history of the disease must be obtained prior to subjects being considered for enrolment.
- 11.1.2.5.** Subject inclusion criteria must also consider GTP treatment groups in terms of demographics, disease stage, rate of degeneration and other relevant clinical parameters.
- 11.1.2.6. Genetic testing and family history:** The sponsors/investigators must provide information from genetic tests (sequencing data) for all clinical trial subjects to establish correct diagnosis and patient selection.
 - i. The mutations must be defined by appropriate bioinformatics pipelines to be functionally relevant and disease causing in each subject.
 - ii. Many conditions may involve functional mutations, insertions or large deletions at different loci within a gene, leading to variability of clinical presentation which may affect the clinical outcomes of the GTP treatment in unknown ways. Prior information regarding

genotype-phenotype correlations should be provided wherever possible to help in trial design and endpoint selection.

- iii. It is strongly advised to test for sequencing validation from family members to define inheritance where relevant.
- iv. The parents/siblings of the affected individuals, particularly minors must undergo the relevant clinical and genetic investigations to establish mode of inheritance and uniformity of clinical presentation.

11.1.2.7. In the event that a genetic mutation is not revealed but loss/gain of function of the causative protein is caused due to epigenetic reasons or promoter mutations, additional tests and justification must be provided for such participants to be enrolled in a GTP trial. Such loss of protein function must be demonstrated and documented. These criteria are typically applicable for complex diseases such as cancers, etc.

11.1.2.8. Subject response to GTP vector and neutralising Ab testing:

Therapeutic potential of the GTP may be limited by adverse immune reactions. Therefore, it is important to test all potential trial subjects for pre-existing neutralising antibodies to the vectors used in the GTP.

- i. Patient selection criteria must include clinical assessment based on levels of pre-existing antibodies/T cell responses to the GTP vector or the gene product. These parameters must be established and patient selection for the trial justified in terms of safety.
- ii. Trial design should incorporate multiple neutralising antibody/T-cell tests and/or other biomarkers at appropriate time points for accurate grouping of the subjects in order to avoid adverse events during GTP infusion (refer to annexure regarding GTP administration for more details).
- iii. Sponsors/investigators must consider developing as a companion diagnostic (*in vitro/ex vivo*) to test for the immune cell and antibody responses to the GTP not just during the patient selection stage, but also during the follow-up period. Eventual progress to commercial applications for GTP may also require such companion tests to support full marketing authorization.

11.1.2.9. Disease severity/staging: The trial sponsors/investigators must provide detailed clinical description of the disease parameters to be considered for enrolling subjects in the trial. In order to do so, the following points are to be considered:

- i. The clinical severity of the disease or disease stage must be recorded meticulously for every subject in any GTP trial. Careful consideration must be given to determining which stage of the disease should the subjects be enrolled in. Very advanced stages of the disease may have unrelated adverse effects during the trial period that may confound the trial results.
- ii. The tissues/cells to be targeted by the GTP must not be fully degenerated at the intervention stage for the GTP to work. However, since advanced disease patients may be more willing to accept the risks of an interventional GTP anticipating clinical benefits, the trial sponsors/investigator, clinical team and local EC must carefully evaluate such subjects in the context of the natural history of their disease.

11.1.2.10. Co-morbidities: Many diseases may have additional co-morbidities involving other organs/tissues depending on the stage and severity of the disease.

- i. Since such co-morbidities may influence the clinical efficacy of the GTP and influence selection of the RoA, they must be carefully evaluated, and patients excluded from the trial based on the extent and perceived influence of such co-morbidities on the expected outcomes or AEs/SAEs.
- ii. Should certain co-morbidities be allowed as part of inclusion criteria, their evaluation should be included as secondary clinical endpoints.

11.1.2.11. Prior therapy history: The participants for a GTP trial may have access to and used various other management options and therapies including recombinant protein therapies or immunosuppressive therapy etc.

- i. The history of all previous and ongoing therapies (standard western medicines or alternative therapy) the subjects have undergone must

be obtained by the sponsors/investigator and evaluated for possible contra-indications to the GTP.

- ii. In particular, prior therapy that may have a chance of precipitating severe immunodeficiency, hepatotoxicity, cardiac or neuronal effects, etc. when GTP is used must be avoided when selecting subjects for GTP trial.
- iii. While treatment naïve patients may be difficult to obtain for a trial, trial investigators must try to do so for first in human trials since the heterogeneity in therapeutic response to GTP may depend on prior and concurrent treatments/alternative therapies.

11.2. Risk evaluation for GTP applications: Almost all GTP have a possibility of unwanted side-effects which may be transient or permanent in nature. Some of the risks may be associated with the nature of the GTP (integrating vs non-integrating, genome editing, immune cell activation and off target tissue damage) or invasive routes of administration (to deliver to the appropriate target tissue). Sponsor/investigator must consider the following:

- 11.2.1.** The anticipated clinical benefit to risk evaluation must be done for each subject enrolled in the trial. Since the risks are typically high, no healthy volunteers/placebo group should be included for a GTP trial.
- 11.2.2.** The risk evaluation and mitigation procedures must be clearly established in the trial design document.
- 11.2.3.** Each participant must be provided with disease related questionnaires as well as the patient information documents and informed consent forms to be signed.
- 11.2.4.** Patient and care giver/relative should be counselled along with detailed patient information sheet and informed consent form describing the risk and benefit parameters provided to trial subjects.
- 11.2.5.** The EC should approve of all the information related to trial provided to participants.
- 11.2.6.** DSMB should monitor the compliance during trial.

11.3. Study Design: *Considerations for Investigational new product and existing gene product.* When designing a GTP trial, it is important to take into account the natural

history of the disease, the patient stratification, disease stage of intervention and duration of post GTP treatment for assessing the endpoints.

11.3.1. Patient numbers for GTP trials: Inherited, familial, rare diseases with defects in the same genetic locus and who qualify all the other parameters for patient enrolment may be a very limited pool. Therefore, it may not be feasible to conduct large scale clinical trials nor have unique subjects for every phase of a clinical trial.

11.3.1.1. Since effects of GTP may be far reaching, investigators must exercise extreme caution and increase numbers of enrolled patients only when initial safety is appropriately established in a small number of subjects.

11.3.1.2. For inherited disease trials, the investigators must carefully estimate the patient cohort based on epidemiological data and justify enrolment numbers based on study design and expected results. In case of rare diseases, the small sample size and inter-patient variability in clinical manifestation and rates of disease progression can reduce the ability of the trial to demonstrate significant treatment efficacy.

11.3.1.3. Therefore, when designing trials with small sample sizes, it is important to try various trial arm designs and statistical models and techniques to extract the maximal possible data points. Multiple endpoints and their weighted reference in the context of clinical features and natural history must be followed to facilitate better justification of study sample size and comparison with other similar studies.

11.3.1.4. For studies involving complex disorders such as diabetes or cancer, if the therapy is targeted towards a specific cell type or activity of specific genes/mutations (over expressing receptors or enzymes, oncogenes, mutated tumour suppressors, etc), patients must be very carefully screened and selected, making the final pool of suitable subjects very well defined. Such trials may have greater numbers.

11.3.1.5. All trial designs must incorporate detailed clinical phenotyping and companion diagnostic and monitoring tests throughout the trial to enable collection of extensive data (including adverse events, efficacy, immune reactions, biomarkers, phenotypic data, etc).

11.3.1.6. All such data will be required for subsequent studies, market authorizations and development of related GTP.

11.3.1.7. For GTPs that have been approved elsewhere (where human data in other populations/races or comparative historical data is already available), such requirement related to detailed study data may be relaxed after appropriate approval by GTAEC.

11.3.2. Trial process design:

11.3.2.1. Randomisation, blinding, masking: Trial sponsors/investigators should consider randomization in early stage development for any first-in-human trials. Concurrent controlled, randomized trial is the ideal for providing GTP safety and efficacy data. This is of particular importance if the intervention is in late stage disease. Therefore, for all such trials, patient population stratification based on disease severity, co-morbidities and genetic information is critical. Randomization based on disease severity is also strongly encouraged. However, considering the difficulties of conducting classical RCTs in gene therapy, the above requirements may not be applicable based on the disease context.

- i. Trial sponsors/investigators must consider as many possible outcome and safety parameters as possible to strengthen support for future market applications.
- ii. GTP administration during a large/multicentre trial must ideally include appropriate masking and blinding procedures to minimise potential bias. If due to the surgical complexity of the route of administration, ethical issues or other clinically relevant reasons, blinding is not possible, the same must be justified in the GTP application.
- iii. If randomisation is not possible, clinical trial data of other GTP trials using other genes (but same gene delivery system) for the same disease may be used for patient grouping. Well characterised natural history of the disease, mechanisms underlying the pathology and other historical comparators may be used by trial sponsors/investigators. However, the same prior information must then be used to set the performance/goal criteria for the GTP trial design.

- iv. To exclude the GTP trials from randomization, the sponsors/investigator must discuss the merits and risks in the context of the Indian patient population with the GTAEC.
- v. Blinding and masking of the clinical team administering the trial is strongly encouraged. However, if the trial design does not allow for such process, the due justifications must be provided in the study design documents.

11.3.2.2. Clinical trial controls: The invasiveness of GTP applications and the mode of action which may cause permanent changes to the target tissues/subject. Therefore, it may not be ethical to include healthy controls in most trials.

- i. If the patient pool eligible for the trial is very small for randomisation, the investigators must consider intra-subject control designs such as contra-lateral location/organ as the control (e.g., in skin disease, eye or ear diseases).
- ii. The additional benefit of such design is the elimination of intra-patient variability and relative comparison of the local therapeutic effect.

11.3.2.3. Patient recruitment process:

The inclusion criteria for any trial must include all the previously discussed parameters and ethical considerations.

- i. Each patient must be provided with disease related questionnaires as well as the patient information documents and informed consent forms to be signed.
- ii. The local IRB must approve of all such forms and track their compliance during trial administration as per the rules of ICMR, DCGI and other regulatory bodies.
- iii. In single-arm trials, historical data and natural history of the disease is critical. In such trials it is important to match the controls and GTP treatment groups in terms of demographics, disease stage, rate of degeneration and other relevant clinical parameters.
- iv. In case of GTP approved elsewhere for the trial to be carried out in

India, the inclusion/exclusion parameters must match the previous data from other trials and the performance parameters must include all the safety and efficacy factors of the previous trials for comparative analysis of final outcome after taking necessary regulatory approvals as defined in section.

11.3.2.4. Enrolment of vulnerable population: Inherited diseases, in particular, the rare diseases often manifest in childhood and hence the paediatric population is a critical part of GTP trial considerations.

- i. In case of minors, immediate relatives/parents/caretakers must be co-signees on the appropriate forms as per Drug and Cosmetics act, 1940 and rules therein.
- ii. Treatment of paediatric patients must first address ethical considerations and conform to the Drug and Cosmetics Act, 1940 and rules therein for conducting clinical trials in vulnerable populations.
- iii. The GTP must provide a direct clinical benefit with minimal increased risk of the investigational procedure.
- iv. The clinical benefit must be justified in each case enrolled in a first-in-human trial which should be equally or more efficacious than available alternate treatment options.
- v. Since paediatric populations have other developmental parameters also to be considered, the safety endpoints (morphometric parameters, developmental milestones) in trial design must consider the same in their trial design.

11.3.2.5. Withdrawal process from GTP trial:

- i. In any clinical trial the autonomy of patient is of utmost importance.
- ii. Patient can withdraw from trial any time before the administration of GTP without prejudice to their ongoing treatment.
- iii. However, once GTP is administered, s/he shall remain part of clinical trial and it is advisable that adequate follow-up of the

patient be carried out after GTP administration to accrue long-term data, risk and benefit to the patient.

11.3.2.6. GTP vector choice: For each gene to be used as therapy for a particular disease, there may be a variety of possible vectors for use.

- i. Detailed description of the GTP vector and its characteristics must be described with justification for its selection in a particular disease. The GTP vector selected must be chosen for its delivery efficacy to the concerned target tissue in the disease.
- ii. Each trial can use only one GTP vector type (or strain or serotype or nanoparticle, etc) for delivery.
- iii. The choice of vectors must be defined from appropriate pre-clinical study designs and using historical comparators from other trials performed for other genes for the same tissue/organ.
- iv. Multi-arm trial designs to compare multiple GTP vectors for delivery efficiency or therapeutic efficiency must incorporate in depth justification from pre-clinical animal testing in both small and large animal models to establish the need for such a design in humans.

11.3.2.7. Route of administration (RoA): The trial sponsors/investigators must provide adequate justification for choosing a certain RoA.

- i. Pre-clinical data providing evidence of efficacy with a certain RoA must be provided. It is strongly advised to study multiple RoA in appropriate disease specific pre-clinical models to determine their relative efficacies.
- ii. Evidence from other similar clinical trials of GTP validating the use of a particular RoA should be provided. If the RoA is first-in-human, then detailed safety endpoints relevant to the RoA must be described in the application and discussed with the GTAEC.

11.3.3. Dose Selection: Establishing the appropriate dose range is imperative to the trial design for any GTP undergoing clinical development.

11.3.3.1. For GTP approved elsewhere, the data from prior trials should be used

to establish dose ranges. The dose selection should be based: on either existing pre-clinical disease model data (minimal toxicity and maximal efficacy dose), or prior trial data with similar GTP and experience in related patient populations referencing all published data in the domain.

11.3.3.2. Where prior human data with a particular gene/vector design and its associated GTP is unavailable, or first in human trials, the *in vitro* evaluation and the animal model data is the only source of informing dose selection. The trial sponsors/investigators must consider multiple readouts from such experiments and a wide range of doses in the pre-clinical models to describe the expected expression efficacy and side effects of the doses administered.

11.3.3.3. Information from biomarkers and companion diagnostics: Information from biochemical assays and enzymatic kinetics should be used in predictive modelling to estimate the starting dosages in human applications using allometric scaling.

- i. In order to aid in dose estimation as well as provide objective evidence of the safety and therapeutic efficacy of the GTP, trial sponsors should design biomarker-based tests as surrogate readouts.
- ii. The GTP development programs should make use of existing knowledge about the clinical pathophysiology, the disease progression and published investigations regarding the molecular profile and biomarkers that associate strongly with disease stage or treatment response can be used for such tests.
- iii. These tests should typically be done from available body fluids or tissues to aid in dose selection, patient selection and GTP efficacy monitoring along with other clinical investigation.

11.3.3.4. Dose escalation: For early phase and first-in-human studies, multiple dose levels to determine the optimal therapeutic dosage is recommended.

- i. The recruitment of patients and GTP administration should be staggered (refer to annexure on GTP administration).

- ii. Adequate justification for the dosage selected in trial design and the appropriate readouts for efficacy and safety in the context of historical comparators and natural history of the disease has to be described.

11.3.3.5. Efficacious dose: The efficacious dose of GTP must be defined based on the data from early phase trials before planning next phase.

- i. The efficacy determination should take both the GTP expression (molecular or biochemical readouts) and the clinical improvement efficacy (refer to section on therapeutic and safety endpoints).
- ii. The safety and efficacy readouts as well as associated clinical, molecular and biomarker readouts will enable the sponsors/investigators to define the maximal efficacious dosage with minimal toxicity.

11.3.3.6. Effect of RoA on dose selection: Trial sponsors/investigators should take into account the RoA in their prediction of toxicity associated with the dosage. Direct local delivery, immune privilege of the target organ and heightened immunoreactivity of the patients with advanced diseases are important considerations when determining the efficacious dosage.

11.4. Immunosuppression: Immune suppression is an important component to be addressed in clinical trial design. Treating diseases by GTP may induce an immune reaction immediately post introduction to the vector or the gene product. The method and RoA of the GTP may independently cause an immune response which may be further accelerated due to the stage of the disease. Such immune response may severely reduce the efficacy of the GTP and cause SAEs. In addition, certain RoA may be more immunogenic than others (systemic delivery vs direct local) and hence careful consideration must be given to reduce the immune response. This is particularly important in the case of therapies that activate the immune system (immunotherapies, CAR-T cells, etc) where immune related SAEs are noted to be quite common.

11.4.1. Transient immune suppression to curb the immediate immune reaction should be considered as part of the trial design to improve patient safety, GTP uptake and subsequent efficacy.

- 11.4.2.** In the event of using the GTP known to activate immune response in humans, it is required to have an effective immune suppression protocol as part of the trial design.
- 11.4.3.** In the event of using new GTPs where the clinical data is not available, appropriate transient immunosuppression protocol should be implemented on case to case basis.
- 11.4.4.** Medical history and current medications have to be taken into account when introducing immunosuppressive regimens.
- 11.4.5.** In gene therapies expected to lead to immunosuppression (eg. Auto immune diseases), additional immunosuppression, transient or long term should be carefully considered and justified.
- 11.4.6.** Those subjects already on immunosuppressive drugs need to be carefully assessed and monitored in trials where further immunosuppression may be required.
- 11.4.7.** Dosage, type and duration of the immunosuppression must be thoroughly discussed by the clinical team and described in the context of the disease supported by data from previous trials and pre-clinical data. In addition, tests to determine the status of immunosuppression and management modalities for SAEs associated with the regimen must also be provided.
- 11.4.8.** The clinical team must be well equipped and have established SOPs to handle CRS (cytokine release syndrome), off target organ toxicities (neurotoxicity, myotoxicity, hepatotoxicity, etc) and infections due to the immunosuppression.

11.5. Requirements for Safety Assessment Considerations:

- 11.5.1. Safety endpoints:** GTP may have unforeseen toxic reactions in the recipient. All GTP clinical development plans must include a detailed and appropriate monitoring plan to protect the trial participants against any AEs and SAEs.
 - 11.5.1.1.** In case of GTPs previously associated with AEs and SAEs, the clinical team and trial administrators must have an appropriate management plan in place based on prior experience.
 - 11.5.1.2.** In case of first in use GTPs, the management plan should be devised based on clinically relevant knowledge of the disease and patient responses.

- 11.5.1.3.** The monitoring plan should include information from pre-clinical toxicology studies and its outcomes (knowledge of the GTP effect, CMC information and risks associated with RoA etc).
- 11.5.1.4. *Dosage considerations for safety:*** If the experience with a certain GTP and RoA is limited, first-in-human trials should stagger consecutively enrolled subjects as well as the different dose cohorts. This will allow appropriate monitoring of any SAEs in individual patients and limit the number of subjects that may be exposed to an unforeseen safety risk (for more information, refer to annexure on GTP administration).
- i. Trial sponsors are strongly advised to confer with the GTP advisory committee regarding this aspect of trial design.
 - ii. In early phase trials, study halting criteria for any observed incidence of SAEs must be included to limit subject exposure to adverse events.
 - iii. Properly designed study halting rules will allow for quick protocol amendments by the sponsors, alter the dosage or RoA and reduce risks due to GTP.
- 11.5.1.5. *Immunological endpoints:*** All GTP induce some innate and adaptive immune responses in the administered subjects. The response may be directed to the vector or the transgene product.
- i. The trial sponsors must develop monitoring tests for all such responses. Post infusion of GTP, monitoring of CRS, neurotoxicity or myotoxicity (particularly in case of CAR-T cell therapy or certain immunotherapies) must be closely monitored and immediately mitigated.
 - ii. Both neutralising and non-neutralising responses, antibody and T-cell based should be monitored. This is particularly important if the GTP needs to be re-administered or the subject is part of a staggered dose escalation arm.
 - iii. The immune reactivity data must determine the decision for re-administration or the choice of an alternate delivery vector or RoA.
 - iv. Finally, trial design in early stages must consider the potential for vector shedding, vector accumulation, etc and consequent effects.

11.5.1.6. Insertional mutagenesis, off target effects: Therapies with GTP depend on introduction of genetic material or modification of the target cells' DNA sequences to achieve clinical benefit. Therefore, there is a risk of causing unintended off-target effects due to the GTP in the host DNA.

- i. Lentiviral or retroviral introduction carries the most risk of insertional mutagenesis and is therefore most advisable for ex-vivo applications wherein the modified cells must be checked for random insertional mutagenesis and establish the risk for teratoma formation.
- ii. Certain GTP transgene products, when expressed at high levels may activate alternate signalling mechanisms harmful to the tissue or the subject as whole. Such risks must be defined based on known functions of the gene and natural history of the disease.
- iii. In particular, for GTP that causes knockdowns or gene editing, it is critical to obtain information regarding off-target effects on other genes apart from the intended target genes.
- iv. Trial sponsors must provide sequencing data from manipulated cells and broad gene expression or protein profiling to address such concerns regarding off-target effects during the trial phases. Therefore, the choice of vector and ROA depend on the appropriate risk assessment in the context of unintended off target mutagenesis.

11.5.1.7. Systemic co-morbidities: Effects of GTP delivery away from the local target tissues must also be evaluated.

- i. Immediately post intervention with a new GTP, additional systemic parameters such as liver and kidney function, cardiac function, lymphadenopathy, splenomegaly, teratoma formation, etc must be considered to be assessed to determine the safety of the subjects.
- ii. Risk of germline transmission must also be addressed by the trial sponsors in their application.
- iii. In the case of existing GTP, testing of co-morbidities may be limited if prior data from other clinical trials or appropriate pre-clinical data is presented with details and justification to the GTAEC.

11.5.2. Efficacy considerations/endpoints: Like clinical trials for any drug, GTP trials also must demonstrate short and long-term clinical benefit. Since GTP entail certain exclusive characteristics, typically expression of a protein product that is new to the body, the function of the product, its levels and localisation may be quite distinct from regular drugs or replacement therapies.

11.5.2.1. The therapeutic endpoints for GTP trials must include assessment of bioactivity of the GTP in addition to clinical parameters testing functional improvement in disease parameters.

11.5.2.2. For many rare diseases undergoing first-in-human trials, there may not be well-established efficacy endpoints that can be assessed directly in patients (due to lack of access to the tissue). Therefore, selection of surrogate efficacy endpoints such as functional improvement, etc is of utmost importance and trial sponsors must justify these surrogate endpoints. Sponsors/investigators are strongly advised to discuss these in detail with GTAEC during the trial design stage.

11.5.2.3. For GTPs approved elsewhere, the trial must include the same endpoints which were used in the prior human trials. However, change in design of endpoints due to new knowledge, different patient population characteristics or newly available monitoring mechanisms are also welcomed to be discussed with the GTAEC and incorporated.

11.5.2.4. Disease specific endpoints: Primary clinical endpoint design should utilise existing information on natural history of the disease and the change in pathology, cellular and tissue morphology and function with increasing severity. Since early trials will typically include stage specific controls as well, the endpoint design must allow for informative differences to be illustrated between cases and controls.

- i. Clinical measurements of disease specific aspects/characteristics must be done at multiple time points longitudinally during the GTP trial to enhance the data quality and make the trial results clearer.
- ii. Such data will be useful for further improvements in trial designs in subsequent studies or for aiding to fast-track towards market authorisations.
- iii. Trial sponsors must include measurements of the same clinical endpoints for a few time points prior to GTP introduction as well

to establish the historical parameters that can ensure proper assessment of the therapeutic benefit of GTP.

11.5.2.5. Biochemical, enzymatic, sequencing based endpoints for gene transfer:

Since all GTP entail the production/alteration of a new protein, biochemical or enzymatic tests to prove the specific alteration is a necessary endpoint.

- i. The assays must be developed for direct measurement from tissue biopsies, bodily fluids, etc or by measurement of enzymatic substrates or their by-products.
- ii. The trial sponsors must consider methods that are minimally invasive which can allow for denser monitoring and therefore be more informative.
- iii. In addition, for GTP that involve gene editing or insertions, investigators must objectively assess the alterations induced by GTP at the genomic level by appropriate methods.
- iv. The intervals at which these endpoints are to be incorporated in the trial design must be provided with appropriate clinical justifications based on characteristics of the GTP and disease history.

11.5.2.6. Effective therapeutic improvement threshold: The effective therapeutic threshold or performance goals of the GTP must be clinically defined prior to commencing trial. These criteria must have due clinical justifications.

- i. Improvement in specific patient functions must be quantifiable and the trial design must include multiple parameters in continuous variable format (scoring) to allow for detailed statistical modelling.
- ii. Trial sponsors are encouraged to consider as many different criteria as possible since a few primary criteria may not show differences early enough in the trial period to allow for course corrections if necessary.
- iii. Sponsors must also consider the disease stage when designing these criteria. Note that in late stage disease, the effects of the GTP may be masked due to severity of the pathology and tissue damage.

Therefore, sponsors must provide criteria that allow for objective assessment of the GTP function.

11.5.2.7. Novel readouts: Since GTPs confer a new molecular function into the target cells/tissues, traditional clinical endpoints may not always be as informative. For many of the rare diseases targeted by GTP, traditional clinical readouts may not be available and hence, sponsors are strongly encouraged to establish novel readouts for therapeutic efficacy. These novel endpoints may be discussed with the GTAEC on a case to case basis depending on the disease.

11.6. Follow up time period: In general, since GTP introduces new genetic elements or new alterations, therefore, long term follow-up is strongly recommended.

11.6.1. Ideally, a follow up of at least 5 years on a case to case basis and post marketing follow up of 10 years is recommended.

11.6.2. The time period may be different for certain diseases based on the natural history, disease pathophysiology or clinical sequelae and that must be justified by the trial sponsors in their application.

11.6.3. While all the follow up tests and parameters used in immediate follow ups may not be necessary or feasible in long-term follow up, the design for the same must be informative and justified.

11.7. Re-administration of GTP: In the event that a certain dose group in the GTP trial was tolerated from the safety perspective but did not achieve clinical efficacy to the desired level, GTP re-administration may be considered.

11.7.1. However, the immune response to the GTP and the gene product has to be evaluated in detail, presented and discussed with the GTAEC.

11.7.2. Same GTP may be applied only if there is no evidence of immune response at the site of therapy and systemically in the patient over a reasonable follow up period (1-2 years).

11.7.3. Thereafter, the choice of altering the GTP type (different serotype, different vector type, different gene or other pharmacological intervention) must be made on the basis of sound scientific evidence and rationale.

11.7.4. Prior knowledge regarding re-administration must be provided using pre-clinical models to assess safety. Immunosuppression regimes must be

considered, and expert opinions provided.

- 11.7.5.** GTAEC may ask for additional safety tests, dense clinical monitoring and recommend seeking additional expert opinions. GTAEC recommendation will be mandatory for any such protocol additions or new applications (where treatment cohort has previously treated subjects).

11.8. Data collection and management:

- 11.8.1.** All data collection and security must follow the Drug and Cosmetics act, 1940 and rules therein.
- 11.8.2.** Data integrity, data entry and data completion must be time bound and strictly regulated.
- 11.8.3.** The clinical trial design must incorporate the data entry and security processes in the application.
- 11.8.4.** Patient data or videos must be stored in secure servers with access control.
- 11.8.5.** Periodically updated trial data should be provided to the local EC and DSMB to assess progress.
- 11.8.6.** Based on periodic trial summaries and or severe adverse events (SAE)s, the DSMB, EC may recommend stopping or putting on hold the clinical trial and report the same to CDSCO and GTAEC.

11.9. Patient Experience (pre and post experience: Improvement in the patients' quality of life (QoL) is the primary goal of every therapy. Therefore, including patient experience parameters and QoL measurements is critical to trial designs.

- 11.9.1.** Trial sponsors should consider well designed questionnaires addressing various aspects of the patients' experience bearing in mind the natural history of the disease, associated co-morbidities, effects on both physical and psychological aspects.
- 11.9.2.** The questionnaires must be used at time points prior to administering GTP in order to establish baseline thresholds.
- 11.9.3.** Existing questionnaires used in OPDs or similar trials may be used as references.
- 11.9.4.** The sponsors must also describe the statistical modelling to be used to analyse such patient experience data for future studies and/or marketing applications.

11.10. Training and qualification requirements for GTP clinical trial: The sponsor performing GTP must include a clinical team well versed in the disease field with documented experience.

- 11.10.1.** If the RoA is novel or very invasive, the clinical team must have the capacity to perform the same and minimise risk to subjects as well as manage unforeseen complications.
- 11.10.2.** Particularly for immune targeting or immune activating therapies such as tumour targeting immunotherapies (such as CAR-T cells), the immediate post treatment immune reactions are common and severe, requiring specialist training and availability of certain drug classes (e.g. IL6 receptor antagonists, etc) to mitigate SAEs.
- 11.10.3.** The clinical team also must have established procedures and mechanisms in place to provide long term care to patients in a GTP trial.
- 11.10.4.** The team should also include a GTP expert or collaborate with the GTP producer who can provide guidance regarding the GTP characteristics relevant to clinical management and patient safety.
- 11.10.5.** Investigators involved in clinical trials must be trained according to GCP ICH standards and as per the Drug and Cosmetics act, 1940 and rules therein for conducting human trials.

12. International Collaboration and International procurement of GTPs

Research involving GTP, is an emerging field of biomedical science and may require national and international collaboration. Such collaborations help the participating institutions for advancement of the field, capacity building and global competence. Participating institutions should consider the following:

- 12.1.** National guidelines and regulations of respective countries shall be followed.
- 12.2.** All international collaborations require approvals of the respective funding agencies followed by approval from the HMSC as per Government of India Guidelines (Available at <http://icmr.nic.in/guide.htm>).
- 12.3.** In situations involving a conflict (scientific and/or ethical) between the collaborators, the existing Indian guidelines, acts and regulations shall prevail for the work to be carried out in India.

- 12.4.** Funding agencies/sponsors shall ensure that certification provided by the collaborating country fulfils the requirements as laid down in these guidelines. For example, all ICMR funded international projects are required to obtain clearance from the HMSC. Similar clearances would need to be obtained if the trial/study is supported by other public/private organizations.
- 12.5.** The components of GTPs, particularly the plasmid constructs or DNA sequences imported must be approved by the IBSC and RCGM prior to development of GTPs.
- 12.6.** Any GTP that is imported in an unaltered form and whose safety, efficacy and therapeutic benefits in human has already been demonstrated outside India may be permitted for possible clinical trials in India on case by case basis subject to prior approval of GTAEC and CBBTDEC, CDSCO.
- 12.7.** Any GTP of foreign origin or its modified variants that will be first in human use is not permissible for direct first in human trials in India.
- 12.8.** Imported GTPs or its modified variants must undergo preclinical animal model studies with due approval of RCGM followed by GTAEC and CDSCO to apply for first in human trials in India.

13. Awareness and Education of Stakeholders

- 13.1.** It is the democratic right of the people to be aware of treatment modalities and the risks versus benefit of new/upcoming technologies such as cell-based therapies including gene therapy. The scientific community including scientists and clinicians working in the field, policy makers including regulators own the responsibility to create awareness and update about the rightful status of the GTPs and their applications on the basis of peer reviewed scientific evidences.
- 13.2.** Public awareness needs to be created through periodic interactions with the public/stakeholders across the country. The focus of such interactive sessions will be to educate the masses so as to avoid their exploitation and to provide a forum for free and frank exchange of views. Different print and electronic media modules can be exploited to this effect.
- 13.3.** Continuous education module needs to be introduced for updating the medical and scientific community.
- 13.4.** The status of new scientific developments and innovative technologies, ethical issues related to these technologies and regulatory pathways need to be ideally a part of the curriculum for medical graduates

14. Unapproved Practices Involving / Claiming Gene Therapy and Publicity / Advertisements in All Media Including Electronic and Print

It may be noted that actions can be taken against the erring clinicians/entities as per the following existing rules and regulations.

- 14.1.** Unapproved practices, advertising and publicity through any mode by clinicians is not permitted as per Indian Medical Council (Professional Conduct, Etiquettes and Ethics) Regulation and its amendments. It is mandated that the MCI and Medical Councils of the respective state should initiate action on the erring clinicians for violation of code of ethics prescribed by them either taking *suo moto* cognisance or acting on any complaint received by them.
- 14.2.** The Drugs and Magical Remedies (The Objectionable Advertisements) Act- 1954 – prohibits misleading advertisements relating to drugs and magical remedies. DGHS and relevant state authorities are mandated to take necessary action for violation of this act.
- 14.3.** The advertisement of treatment of several diseases as listed in Schedule J of Drugs and Cosmetics Act, 1940 and Rules therein (*Annexure VII*) is not permissible. Hence publicity claiming available cure for these conditions using GTPs is prohibited. CDSCO, DGHS and relevant state authorities are mandated to take necessary action for violation of this act.
- 14.4.** No advertisement which violates the code for self-regulation in advertising, as adopted by the Advertising Standards Council of India (ASCI), Mumbai for public exhibition, from time to time, shall be published. Available at https://ascionline.org/images/pdf/code_book.pdf

15. Periodic Review of Guidelines

The field of gene therapy has seen rapid strides both in basic and translational aspects. These guidelines reflect the minimum requirements for the potential use of GTPs and mirrors current state of the art in this field. With the unfolding of new developments and knowledge in this dynamic field, it is essential to periodically review and update the guideline document. Accordingly, periodic changes to specific clauses and sections will be notified in the form of amendments. The GTAEC will determine from time to time the need and mechanism for implementing revisions to the document.

Glossary

academic clinical trial- a clinical trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic or research purposes and not for seeking approval of the Central Licencing Authority or regulatory authority of any country for marketing or commercial purpose adenovirus- family of viruses with DNA as genetic material that do not integrate their genome into the DNA of host cells they invade

adeno-associated virus- genus of dependoviruses (of family Parvoviruses) which are not non-pathogenic (e.g. adeno-associated virus 2)

adventitious agent- microorganisms that could be unintentionally introduced during a manufacturing process

allogeneic- refers to cells or tissues that are obtained from two different individuals of the same species and hence immunologically incompatible

animal model- an animal that naturally displays or have been generated to model a human disease

antibiotic- a type of antibacterial substance (medicine such as penicillin) that inhibits the growth or kills the bacteria

antibiotic resistance- the ability of bacteria to resist the effects of a medicine that was once successful in treating infections caused by them

antibody- produced mainly by plasma cells that is used by the immune system to neutralize pathogens, also known as an immunoglobulin

antisense oligonucleotides- short nucleotide sequences that bind to the target RNA sequence

aptamers- short nucleotide or peptide molecules that bind to a specific target molecule

autologous- refers to cells or tissues that are obtained from the same individual

bacteriostasis- inhibition of the growth of bacteria without destroying them

bio-activity- effect of a given chemical (eg. drug) or biological (e.g. vaccine) agent on living cells

bio-distribution- refers to tracking of compounds of interest in an experimental animal or human subject

biohazard- refers to biological substances that pose a threat to the health of all living organisms

bioinformatics - a field of study that involves the integration of computers, software tools, and databases in an effort to address biological questions

biomarkers- measurable indicators (e.g. molecules) of the severity or presence of a disease state, useful in predicting diagnosis and disease progress

blood-ocular barrier- physical separation between the eye and surrounding blood vessels

bovine- primarily refers to cows, and oxen, but also includes goats, sheep, bison and buffalo

CAR-T cells- reengineered cells bearing chimeric antigen receptors on their surface used in cancer immunotherapy

cationic lipid- positively charged lipids that bind to DNA molecules forming lipoplexes, used as delivery vehicles

cationic polymer- positively charged polymers that bind to DNA molecules forming polyplexes, used as delivery vehicles

causative gene- a gene that is responsible for causing a specific disease cell culture in the laboratory

cell line- a cell culture from transformed primary cells that is generated in the laboratory dish after isolation of cells from a primary source (plant, animal or human)

clinical trial - relates to interventions that are carried out in human beings, after a complete assessment of intended benefits and potential risks in animal models

CRISPR- clustered regularly interspaced short palindromic repeats are DNA sequences found within the genome of prokaryotes, and are used in genome editing along with enzymes called CRISPR-associated nucleases (most commonly Cas9)

carcinogenicity- the process which leads normal cells to become cancer cells

collagenase- an enzyme that breaks the peptide bonds in collagen, also used to dissociate cells in culture

cryopreservation- method of freezing cells, tissues, organs at ultralow temperatures, usually in liquid nitrogen tanks at a temperature of – 196°C

cytokine- a small protein that influences the behaviour of neighbouring cells by cell signalling

cytolytic virus- an infection-causing virus that invades and kills host cells

cytopathic virus- a virus that causes structural changes in the host cells

cytotoxicity- refers to the ability of being harmful to the cells

DNA- deoxyribonucleic acid, a chemical molecule often referred to as the 'fundamental unit of heredity'

DNase- an enzyme that breaks the phosphodiester bonds in the DNA backbone

DNA vaccine- vaccine that contains genetic information of a specific bacterial or viral pathogen used for immunization purpose

dose-escalation- a gradual increase in the dose of a drug or any other treatment in order to improve its tolerability or maximize its effect

efficacy- the ability to produce a desired result

endogenous- having an internal cause or origin

endophenotype- any hereditary characteristic that is normally associated with some condition but is not a direct symptom of that condition

endophenotyping- refers to the building, recording and analysis of endophenotypes

endotoxin - a component of the outer membrane of gram-negative bacteria, often associated with both pathogenic and non-pathogenic ones

end-point assay- an enzyme-based assay that estimates the amount of material by measuring the quantity of a substrate consumed or product formed over the course of a reaction

enzyme kinetics- the study of several characteristics of chemical reactions that are catalysed by enzymes

epigenetic- relating to heritable changes in gene expression that do not involve alterations in the DNA sequence

episome- a non-essential genetic element of either bacterial or viral origin that is capable of independent existence within the host cell

exogeneous- having an external cause or origin

exosome- cell-derived vesicle that are present in various body fluids such as blood, urine, etc.

extra-genomic- genetic material that is not part of an organism's genome

ex vivo - (of a process) performed outside an organism's natural environment, results of which can be applied to the whole organism

foetal bovine serum- derived from clotted blood of bovine fetuses, widely used as serum supplement in culturing mammalian cells

first-in-human trial/clinical use- refers to the first-ever experimentation in humans, often called a Phase I clinical trial

foamy virus- retroviruses of the genus Spumavirus that have a complex genetic structure some of which are not harmful to humans (e.g. human foamy virus)

fungistasis- inhibition of the growth of fungi without destroying them

gamete- an organism's reproductive cell, e.g. sperm and egg

gene deletion- a mutation that is characterized by removal of one or more nucleotides from a DNA sequence

gene knock-in- insertion of a gene either by one-for-one substitution in a genetic locus or a sequence not found within the locus

gene knock-out- deletion of a gene from its endogenous locus in an organism

genetic mutation- a permanent alteration in the DNA sequence leading to an organism's phenotypic change

genome- the complete set of genes or genetic material that is present in all the cells of an organism

genetic modification- a process of altering the genetic makeup of an organism, synonymous with genetic manipulation

genome editing- a process in which DNA is inserted, deleted, modified or replaced in the genome of an organism, synonymous with genome engineering

genotoxicity- refers to the ability of being harmful to the host genome

genotype- pattern of genes in an organism's DNA that is responsible for a particular trait

germ line- a series of germ cells that have been developed through successive generations of an organism

growth factor- a naturally occurring substance such as a protein or a steroid hormone that stimulates cellular growth, proliferation and differentiation

haem-adsorbing virus- a virus which infects cells that are selectively attached to red blood cells (*in vitro*)

helper plasmid- a recombinant plasmid that contains one or more genes essential of viral replication and assembly

hepatotoxicity- refers to chemical or drug-induced liver damage

heterogeneity- state of being diverse in nature or content

herpes simplex virus- a DNA-based virus that causes contagious sores most often around the mouth or the genitals

homologous recombination- mechanism by which genetic sequences are exchanged between two identical DNA molecules

immunodeficiency- a state in which the immune system's ability to fight infectious diseases and cancer is either compromised or completely absent

immunogenicity- the ability to provoke an immune response in the body of a host animal or human being

immune-privileged- ability to avoid an immune response

immunoreactivity- a measure of the immune reaction caused by an antigen

immunosuppression- partial or complete suppression of an individual's immune response

immunotherapy- therapy that works by stimulating or restoring the ability of the host immune system to fight infection or disease

inducible promoter- a promoter that has the ability to turn gene expression on or off at certain stages of development of an organism or in a particular tissue

insertion mutation- a mutation that is characterized by addition of one or more nucleotides into a DNA sequence

insertional mutagenesis- the ability of viruses or other foreign genetic material to cause mutations in the host genome by integration

intrathecal- a route of administration by injection through the spinal cord

intron- long stretches of non-coding DNA present between the coding regions (exons) in a gene

in utero- referring to the uterus or womb

in vitro- (of a process) performed outside a living organism, such as a test tube or a culture plate

in vivo- (of a process) performed inside a living organism

knockdown- reducing the expression of a gene without completely deleting it

lentivirus - genus of retroviruses that cause chronic and deadly infections in mammals (eg. lymphadenopathy- a disease of the lymph nodes in which they grow abnormally in size, number, or consistency)

miRNA- a small non-coding microRNA that is used in RNA silencing and regulation of gene expression

monogenic- involving or caused by defect(s) in a single gene

morbidity- state of having a disease or health problem

mortality- state of being prone to death

motif- a common secondary structure that could be seen in different nucleic acids or proteins

murine- refers to mice, and other related rodents such as rats

mutant- an organism or a genetic trait that results from a **mutation**

mycoplasma- a genus of bacteria without a cell wall which make them naturally resistant to many common antibiotics

naked DNA- Free DNA, not associated with molecules such as proteins or lipids

nano-composition- a multiphasic material with one of the phases having one, two or three dimensions of less than 100 nanometres

nanoparticle- a microscopic particle in the size range of 1 to 100 nanometres that a number of potential applications in biomedical research

neutralizing antibody- an antibody that protects a cell from an antigen or infectious agent by neutralizing its biological action

non-coding DNA/RNA- DNA/RNA that is not coding its information to proteins

non-human primate- refers to the macaques, and marmosets

non-viral vector- a chemical-based tool used in DNA delivery (eg. nanoparticle)

off-target effect- adverse effect either related or unrelated to the target site

oncogene- a gene with the potential to cause cancer

oncolytic virus- a virus that preferentially infects and kills cancer cells

on-target effect- intended or adverse effect at the target site

open reading frame- the part of a genome that has the ability to be translated

origin of replication- a particular sequence in a genome which marks the start of DNA replication

pathophysiology- refers to the disordered physiological processes that are associated with a disease

pharmacokinetics- the movement of a drug in a living organism from the time of administration to its eventual excretion, as abbreviated in LADME (liberation, absorption, distribution, metabolism, and excretion)

phenotypic rescue- refers to the reversal of a disease phenotype

packaging cell line- mammalian cells that have been transfected with all the viral proteins essential for capsid production and virion maturation, used for packaging gene therapy vectors into live, infectious viral particles

phenotype- expression of an organism's physical characteristics or traits

polyadenylation signal- a stretch of adenine (A) nucleotides typically found at the end of all eukaryotic genes which serves as a signal to stop transcription (mRNA synthesis)

porcine- refers to the domestic pig, often called swine or hog

pre-clinical trial- relates to experiments that are carried out in animal models before translating them into humans

producer cell clone- a packaging cell line that has been established to produce viruses at high titres, used for clinical grade and scale production of viruses for gene therapy

pyrogen- a substance, often released by a bacterium, that causes fever when introduced into the blood

randomization- a method based on chance alone whereby study participants are assigned to either a treatment or placebo group

recombinant virus- a virus that is produced by recombinant DNA techniques

regulatory element- a genetic element that is capable of increasing or decreasing gene expression, such as promoter, enhancer, etc.

replication-competent virus- a virus that is capable of propagating within the infected host cells

replication-defective virus- a virus that is not capable of propagating within the infected host cells

restriction enzyme- an enzyme mostly produced by bacteria that can cleave DNA molecules at or near a specific sequence of nucleotides

retrovirus- family of viruses with RNA as genetic material that can integrate their genome into the DNA of host cells, they invade

ribozymes/deoxyribozymes- RNA or DNA molecules that are capable of catalysing specific biochemical reactions

RNA- ribonucleic acid, a chemical molecule that carries information from DNA to proteins, some of which are 'messengers'

rodent- refers to rats, hamsters, guinea pigs, marmots, and chipmunks

self-complimentary- (of a sequence) refers to the ability to bind to a matching nucleotide sequence

serotype- (of a virus) the variations within a species of bacteria or virus

shRNA- a short or small hairpin RNA, artificially designed in the shape of a hairpin and used in silencing target gene expression

siRNA- a small interfering RNA that is used in silencing target gene expression

splenomegaly- refers to enlargement of the spleen, measured by size or weight

teratoma- a benign tumour that is made up of cells of several different types of tissues, such as hair, muscle, or bone

therapeutic threshold- the minimum level or amount of a therapeutic gene expression that is required to reverse the disease phenotype

therapeutic endpoint- the occurrence of a favourable outcome that signals the end of a therapeutic process

transduction- a virus-mediated gene transfer method used for mammalian cells

transfection- a method used to deliberately introduce naked plasmid DNA into mammalian cells

tropism- (of a virus) the ability to infect many different cells and tissues

tissue-specific promoter- a promoter that controls gene expression in a tissue-dependent manner

transfer plasmid- a recombinant plasmid that contains the therapeutic gene

transcription- first step in gene expression where a sequence of DNA is copied into an RNA

translation- second step in gene expression where an RNA sequence is converted into a protein sequence

transgene- a genetic material that is artificially introduced into the genome of another organism

transgenic animal- an animal that is generated by transferring a gene or genetic material from another species or breed

trypsin- a gut enzyme that is often used as a cell dissociation agent in mammalian cell cultures

viral capsid- protein shell that protects the genetic material of a virus

viral envelope- the outer coat of a virus that is sometimes derived from portions of the host cell membrane

viral vector- A vehicle containing viral genome and capsid that is modified using recombinant DNA techniques to accommodate an exogenous genetic material of interest, used as DNA delivery vehicle or tool

wild-type- phenotype of the typical form of a certain species as seen in nature

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ANNEXURES

Composition and Functioning of GTAEC

The field of gene therapy has gathered pace over the past couple of decades due to the rapid discovery of large numbers of genes which are mutated in a variety of diseases. To develop an ideal strategy to treat various diseases/disorders, it requires a great depth of scientific knowledge to design the gene therapy for human applications.

This document will serve to provide basic framework and entail the requirements thereof for all those who aspire to test advanced therapeutics involving the transfer of genetic material for the purpose of treatment. It is understood that quite a few indigenous and international gene therapy products are at the final stage of development and are expected to be ready for translation soon. The scientists and Industry involved in the field are seeking advice and directions regarding regulatory requirements for preclinical studies and clinical translation of GTPs. The investigators/ Industry needs hands holding for Pre IND guidance and evaluation.

In view of this, a - **Gene Therapy Advisory and Evaluation Committee (GTAEC)** has been constituted and notified by Department of Health Research (DHR), Ministry of Health and Family Welfare, Government of India as an independent body of experts representing diverse areas of biomedical research, concerned government agencies and other stakeholders.

This is a multi-disciplinary and inter-ministerial/inter-agency committee with its Secretariat at the ICMR Headquarters, New Delhi. The main objectives of the committee are i) to serve as an apex advisory body to Government of India for research and development gene therapy field in India; ii) to perform a comprehensive review of the pre-IND and IND applications of GTPs; iii) formulate policies to inculcate scientific and ethical practices amongst stakeholders.

The committee will provide a forum for discussion of issues involved in basic and clinical research and progress in the field. It will also periodically assess the adequacy of the document in light of advancements in the field. The unforeseen issues of public interest can also be referred to it.

1.1. Scope

- 1.1.1. Examine scientific, technical, ethical, legal and social issues in the field.
- 1.1.2. Pre-IND consultations.
- 1.1.3. Review all GTP clinical trial applications and provide recommendations prior to approval from CDSCO, to provide inputs to CBBTDEC.
- 1.1.4. Periodically review and update the guidelines and their possible therapeutic applications keeping pace with global scientific developments in the field.
- 1.1.5. In co-ordination with the CDSCO and keeping in view other existing regulations, set-up standards for safety and efficacy, quality control, procedures for GTP and its licensing/approval.
- 1.1.6. Respond to queries and representations from stakeholders in the community (investigators, industry, R&D Institutions, entrepreneurs, media, patient groups, government agencies etc.).
- 1.1.7. Address suggestions and feedback received from other government agencies and stakeholders.
- 1.1.8. Raise education and awareness amongst the stakeholders.
- 1.1.9. GTAEC will collect all the data related to GTP clinical trials which would help in evolution of knowledge base which will then improve the quality and conduct of clinical trial and their comparison and harmonization with international data.

1.2. Composition

The committee is composed of the following:

Chairman, Alternative Chairman, Member Secretary (ICMR), nominees from MoHFW, CDSCO, MCI, DBT, DST, CSIR, RCGM, BIS, QCI, biomedical experts with relevant experience in gene therapy, GTP or their applications. The biomedical experts group will be drawn from appropriate disciplines such as, but not limited to, gene therapy, haematology, pharmacology, immunology, cell and molecular biology, molecular medicine, microbiology, genetics, developmental biology, clinical medicine and nursing and may be broadened to co-opt sub committees for specific disease area or type of GTP administration. Other members include ethics and legal experts, social scientist, lay-person and women's representative and subject experts as per the domain area of the proposals under evaluation.

- 1.3. **Frequency of meetings** The meeting may take place quarterly, but can be more frequent, as per the needs and requirements.

Clinical Trial Protocol Template

Section	Description
1.	Study title:
	Protocol ID: Phase of the study: Sponsor: Contract Research Organization:
	Investigator/s and Institution/s
2.	Synopsis of the protocol (Summary)
3.	Introduction (including preclinical and clinical experience)
4.	Study rationale (including potential risks and benefits)
5.	Study objectives (primary and secondary objectives)
6.	Study design
	Number of patients
	Eligibility criteria a. Inclusion b. Exclusion
	Study activities: Phase a. Screening b. Treatment c. Post –treatment d. Follow-up
	Schedule of visits and activities at each visit
7.	Withdrawal of patients prior to study completion

8.	Safety assessment <ol style="list-style-type: none"> Definitions Documentation of adverse events Reporting of serious adverse events
9.	Efficacy assessment: Outcome <ol style="list-style-type: none"> Primary efficacy Secondary efficacy
10.	Concomitant Medications <ol style="list-style-type: none"> Documentation of medications – name, dose, duration Intercurrent illness Prohibited medications
11.	Investigational New Entity <ol style="list-style-type: none"> Chemistry Manufacturing and Control (CMC) information Dosage Route of administration GTP preparation and administration instructions Accountability of Investigational drug/product (QA/QC)
12.	Data evaluation/statistics <ol style="list-style-type: none"> Sample size determination Study population analyses Efficacy analysis/methods Safety analysis/methods Adverse events Clinical laboratory studies
13.	Ethical and Administrative Issues <ol style="list-style-type: none"> Informed consent including audio video consent from Patient /Parent/Relative Risks and benefits Approval of EC, IC-SCR (if using stem cells), RCGM, GTAEC and CDSCO
14.	Data and Safety Monitoring Board (DSMB)
15.	Adherence to the protocol <ol style="list-style-type: none"> Protocol deviation/amendment

16.	Data collection, source documentation and retention of patient records
17.	Monitoring of the study and audit
18.	Intellectual Property Rights (IPR) issues (patent obtained/filed)
19.	Confidentiality
20.	References
21.	Enclosures <ul style="list-style-type: none"> a. CMC b. Investigator brochure including background, rationale, product details, pre-clinical study results, human trials, references and publication lists and reprints c. Case Record Form d. Manual for efficacy assessments, safety assessments, laboratory procedures etc. e. Approved patient information sheet and consent form (including audio video consent) f. MOU/MTA in case of national/international collaboration with transfer of biological materials g. Funding of the project/sponsor h. Conflict of interest declaration i. Clearances of EC, IC-SCR (if using stem cells), RCGM, GTAEC and CDSCO j. Charter of DSMB k. Certificate of Registration of EC and IC-SCR (if using stem cells)

* For further reference please see 'New Drugs and Clinical Trials Rules 2019'

Annexure III

Template for Patient Information Sheet & Informed Consent

You are being invited to participate in a clinical trial.

Before you take part in this trial, the study must be explained to you by the sponsor/site investigators and you must be given the chance to ask questions. Please read carefully the information provided here. If you agree to participate, please sign the informed consent form. You will be given a copy of this document to take home with you.

STUDY INFORMATION

Protocol Title:

Site Investigators list:

PURPOSE OF THE RESEARCH STUDY

You are being invited to participate in a research study to xxxxxxxxxxxxxxxx

This study will recruit approximately xxxxxxxxxx from xxxxxxxxxx.

The purpose of the study is to xxxxxxxxxxxxxxxx (followed by study title).

The study will be conducted in the xxxxxxxxxx department at xxxxxxxxxx, (local address of institution). You have been selected as a possible candidate for the study as you are xxxxxxxxxxxxxxxx (explaining diagnosis).

Samples of tissues, blood and/or body fluids (amend as per protocol) may be obtained during the course of the study as per the clinical trial protocol approved by CDSCO. Furthermore, any future commercialization of the discoveries from the study will be done with prior local Ethics Committee approval.

STUDY PROCEDURES AND VISIT SCHEDULE

The study will be conducted at xxxxxxxx. If you agree to take part in this study, you will be asked to undergo the routine diagnostic testing and detailed examination.....xxxx(explain the tests that will be done. Explain if these tests are invasive nor do they require hospital admission). The tests will be conducted during your hospital visit timings as per the schedule to be shared with you as per the clinical trial protocol. You will not be charged for these tests and examination.

Schedule of visits and procedures:

Xxxxxxxxxx(details of the procedures to be followed in each visit)xxxxxxxxxxxxxxxx

YOUR RESPONSIBILITIES IN THIS STUDY

If you agree to participate in this study, you should:

- Be prepared to visit the hospital (name and location) and undergo the procedures that are outlined above.

- Follow up as per clinical trial protocol
- During the trial and follow up period, you should not participate in any other trial/medical treatments without prior written consent of the GTP trial administrators.

WITHDRAWAL FROM STUDY

You are free to withdraw your consent and discontinue your participation at any time without prejudice to you or effect on your medical care. However, you will not be allowed to withdraw from a trial once you have been administered the GTP because you will require to be monitored and all drug effects reported. If you decide to stop taking part in this study, you should inform the Principal Investigator. If you withdraw from the study, the data collected will not be analyzed and will be discarded.

Your doctor, the Principal Investigator of this study may stop your participation in the study prior to GTP administration at any time for one or more of the following reasons:

- Ineligibility for enrolment criterion.
- The study is cancelled/termination before GTP administration.
- Unanticipated circumstances.
- Clinical adverse events.

POSSIBLE RISKS, DISCOMFORTS AND INCONVENIENCES

Xxxxx (explain details of the tests and procedures)

POTENTIAL BENEFITS

Your participation is subject to your explicit consent. Your participation does not entitle you to any financial benefits due to participation in the trial.

SUBJECT'S RIGHTS

Your participation in this study is entirely voluntary. Your questions will be answered clearly and to your satisfaction.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you or your legal representative will be informed in a timely manner by the Principal Investigator or his/her representative.

You have the right to refuse to allow your images or test results to be studied now or saved for future study.

By signing and participating in the clinical trial, you do not waive any of your legal rights to revoke your consent and withdraw from the trial at any time.

CONFIDENTIALITY OF STUDY AND MEDICAL RECORDS

Information collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available. Only your Investigator(s) will have access to the confidential information being collected.

However, the xxx (name of hospital) xxxx, Regulatory Agencies, Institution Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you or your legal representative is authorizing such access to your study and medical records.

Data collected and entered into the Case Report Forms are the property of study sponsor, hospital. In the event of any publication regarding this study, your identity will remain confidential.

COSTS OF PARTICIPATION

There will be no cost to you towards any procedures and tests involved in the clinical trial.

You will be reimbursed for your participation in this clinical trial (as per the decision of the EC).

CLINICAL TRIAL RELATED INJURY AND COMPENSATION

In case of any medical related injury occurring to you, you shall be provided medical care by the institution.

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

WHO TO CONTACT IF YOU HAVE QUESTIONS

If you have questions about this research study and your rights or in the case of any injuries during the course of this study, you may contact the Investigator xxxxxx, (sponsor details, hospital name). Tel: xxxxxx

If you have questions about the study or your rights as a participant, you can call the Institutional Ethics Committee, which is the committee that reviewed and approved this study.

Details of Ethics Committee

Tel: +91.....

Address

INFORMED CONSENT BY RESEARCH SUBJECT

XXXXXX

Principal Investigator,

Sponsor and hospital name and address

Research Subject's Particulars

Name: _____ ID No: _____

Address:

Sex: Female / Male Date of birth: _____ (dd/mm/yyyy)

Nationality: Indian /Others _____ (please specify)

Part I – to be filled by patient

I, _____ (Name of patient)

(ID No. _____)

agree to participate in the above-mentioned clinical trial as described and as per the terms set out in the Patient Information Sheet. The nature of my participation in the proposed clinical trial has been explained to me in _____ (Language / Dialect) by Dr / Mr / Ms _____. (Name of healthcare worker)

I have fully discussed and understood the purpose and procedures of this clinical trial. I have been given the Patient Information Sheet and the opportunity to ask questions about this clinical trial and have received satisfactory answers and information. I clearly understand the nature, risks and benefits of the clinical trial.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reasons and without my medical care being affected.

I **agree** to allow my clinical data/reports/images obtained during the course of this clinical trial to be stored and analyzed solely for the purposes of this clinical trial for a period not exceeding than 15 years from date of clinical trial completion, and thereafter destroyed.

I give my consent to undergo the above-mentioned tests in organ/tissue/etc ...

I **agree** for my information and medical records to be used for clinical trial reporting and analysis.

I understand that ...sponsor/hospital..., Regulatory Agencies, Institution Ethics Committee and Ministry of Health will be granted access to my original medical records, in order to check clinical trial procedures and data, without jeopardizing the confidentiality of my identity. I further understand that by signing this Informed Consent Form, I am hereby authorizing such access to my data/medical records.

In any event of publication, I understand that this information will not bear my name or other identifiers and that due care will be taken to preserve the confidentiality of my identity.

I understand that this consent shall be governed by and construed in accordance with the New Drug & Clinical Trial Rules 2019.

_____ [Signature/Thumbprint(Right/Left)of patient]

_____ (Date of signing)

Part III – to be filled witness, where applicable

(An impartial witness should be present during the entire informed consent discussion if a subject or the subject's legally acceptable representative is unable to read. After the written informed consent form and any written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally representative has orally consented to the subject's participation in the clinical trial and, if capable of doing so, has signed and personally dated the consent form, the witness should sign and personally date the consent form.)

Witnessed by _____ (Name of witness)

_____ (Designation of witness)

_____ (Signature of Witness) _____ (Date of signing)

Part IV—Investigator’s Statement

I, the undersigned, certify to the best of my knowledge that the person signing this informed consent form had the clinical trial fully explained and clearly understand the nature, risks and benefits of his/her participation in the study.

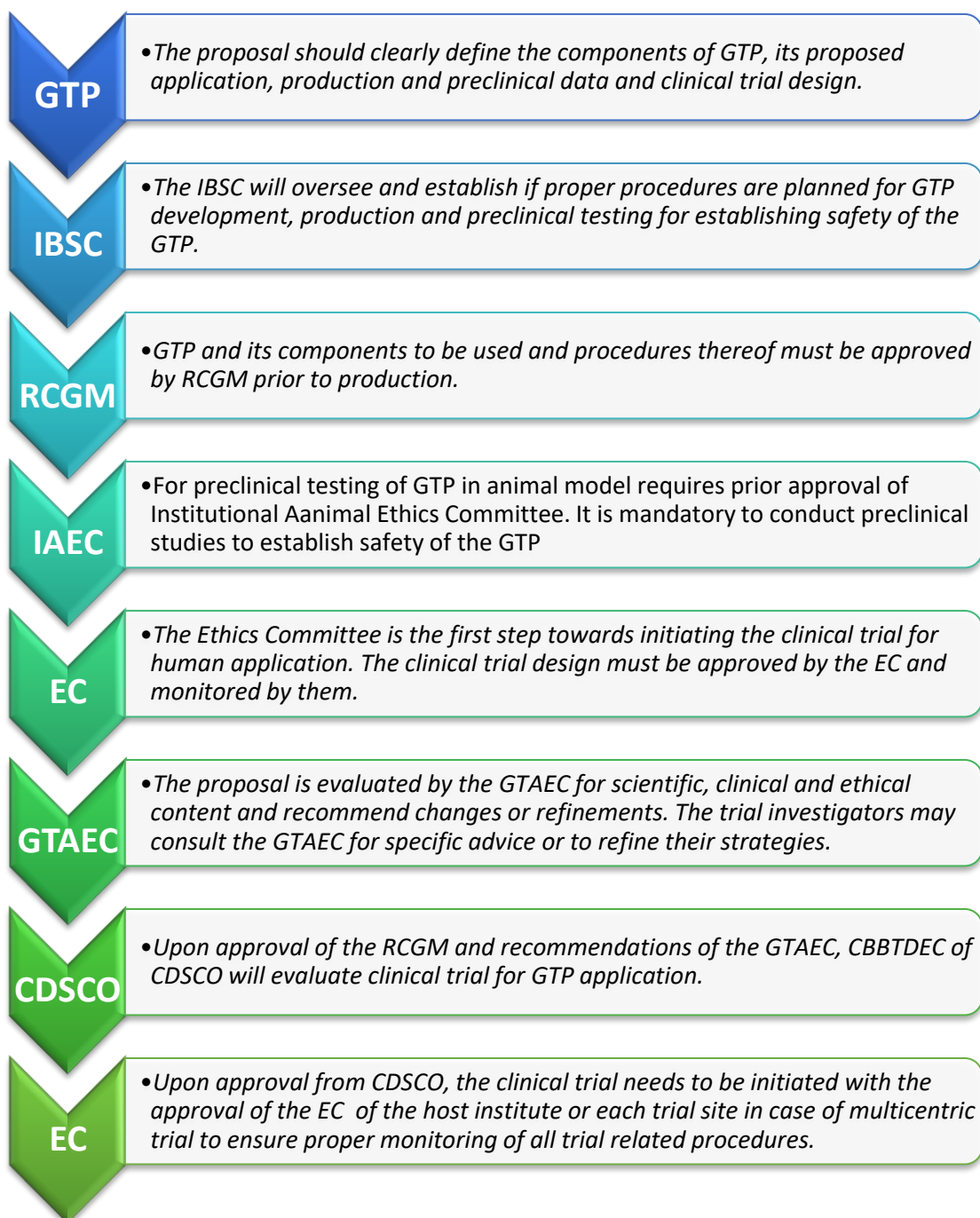
_____(Signature of Investigator)

_____(Name of the investigator) _____(Date)

* For further reference please see ‘New Drugs and Clinical Trials Rules 2019’

Annexure IV

Regulatory Process for GTP Clinical Trials



SCHEDULE J of Drugs and Cosmetics Rules, 1945

Diseases and ailments (by whatever name described) which a drug may not purport to prevent or cure or make claims to prevent or cure.

- | | |
|--|---|
| 1. AIDS | 28. Increase in brain capacity and improvement of memory. |
| 2. Angina Pectoris | 29. Improvement in height of children/adults. |
| 3. Appendicitis | 30. Improvement in size and shape of the sexual organ and in duration of sexual performance |
| 4. Arteriosclerosis | 31. Improvement in the strength of the natural teeth. |
| 5. Baldness | 32. Improvement in vision |
| 6. Blindness | 33. Jaundice/Hepatitis/Liver disorders |
| 7. Bronchial Asthma | 34. Leukaemia |
| 8. Cancer and Benign tumour | 35. Leucoderma |
| 9. Cataract | 36. Maintenance or improvement of the capacity of the human being for sexual pleasure. |
| 10. Change in colour of the hair and growth of new hair. | 37. Mental retardation, subnormalities and growth |
| 11. Change of foetal sex by drugs. | 38. Myocardial infarction |
| 12. Congenital malformations | 39. Obesity |
| 13. Deafness | 40. Paralysis |
| 14. Diabetes | 41. Parkinsonism |
| 15. Diseases and disorders of uterus. | 42. Piles and Fistulae |
| 16. Epilepticfits and psychiatric disorders | 43. Power to rejuvenate |
| 17. Encephalitis | 44. Premature ageing |
| 18. Fairness of the skin | 45. Premature greying of hair |
| 19. Form, structure of breast | 46. Rheumatic Heart Diseases |
| 20. Gangrene | 47. Sexual Impotence, Premature ejaculation and spermatorrhoea |
| 21. Genetic disorders | |
| 22. Glaucoma | |
| 23. Goitre | |
| 24. Hernia | |
| 25. High/low Blood Pressure | |
| 26. Hydrocele | |
| 27. Insanity | |

- 48. Spondylitis
- 49. Stammering
- 50. Stones in gallbladder, kidney,
bladder
- 51. Vericose Vein

Clinical Administration of GTPs

This annexure is meant for reference purposes, the final trial design should include the following points but not limited to these only.

This section outlines, in brief, the general principles for the site/Institution or investigator/clinician performing GTP administration to human participants and the general procedures thereof. All investigators must refer to the main guidelines document when designing any GTP trial. The GTP and the trial design must have prior approval from all regulatory bodies (EC, GTAEC, CDSCO). The precise GTP administration procedure may vary case to case, but the investigators/clinician should bear the following in mind:

- 1. GTP:** The identity and integrity of the GTP to be administered should be clearly established prior to patient preparation or admitting the patient for the procedure.
 - 1.1.** Only subjects that qualify after following the guidelines of patient recruitment (inclusion/exclusion) may be infused with GTP.
 - 1.2.** The GTP to be administered must have clear labelling with appropriate release criteria recorded prior to administration.
 - 1.3.** Visual and other quality checks must be performed and recorded on GTP vials/containers to ensure safety.
- 2. Clinical Trial investigator:** The trial investigator(s) must have appropriate experience with the disease and have complete knowledge of the GTP administration protocols, the safety and monitoring procedures.
 - 2.1.** The investigators(s)/sponsors as well as the local trial site investigator must assume responsibility for ensuring the right GTP at the approved dosage and RoA is infused in the selected subjects accurately following the approved trial protocols.
 - 2.2.** They are also responsible for maintaining all records pertaining to each step of administration and all other relevant parts of the trial. The investigators must keep the EC informed regarding any AE/SAE or deviations.
 - 2.3.** The trial site investigatory team must include clinicians, scientists, nursing staff, trained medical staff for emergencies and counsellors.
- 3. Clinical Trial Site:** The trial site must have all the clinical expertise and infrastructural requirements for administering GTP.
 - 3.1.** These requirements include but are not limited to clinical equipment to diagnose and monitor the disease in patients, clean and approved operating theatre for GTP

infusion with surgical and/or other equipment required for the procedure.

- 3.2. The site must have the infrastructure to safely store, appropriately monitor and handle the actual GTP vials/containers.
- 3.3. The site must have a local EC which is registered with ICMR for maintaining oversight.
- 3.4. The clinical team at the site must have demonstrable expertise/training for patient selection, patient, monitoring, GTP administration.
- 3.5. The site team must have demonstrable ability for handling AE/SAE including emergency staff and emergency medical equipment.
- 3.6. Since the local site trial administrator/PI will be responsible for recruiting and monitoring the patients, they must also counsel the patients and families in appropriate local languages regarding all aspects of the trial including risks.
- 3.7. Patient and family informed consent must be taken by the site through written and video procedures as per approved trial protocol and stored safely.

4. Pre-administration procedures: The following points provide general principles for pre-administration procedures which have to be further refined and specialised depending on the disease and the GTP.

- 4.1. For first in human GTP administration, the subjects must be admitted at least 24-48 hours prior to the actual GTP infusion.
- 4.2. Patients' vitals, immunological and serological status must be recorded through proper biological tests as determined in the final approved protocol.
- 4.3. Care must be taken to ensure the patients do not have any other confounding issues including infections, recent surgeries, physical or mental stress.
- 4.4. Any GTP specific or disease specific monitoring tests (specific biomarkers, etc) should be performed during this time to aid in determining final outcomes and minimise potential risks.

5. GTP administration to patient:

- 5.1. The GTP administration must be performed in an operating theatre with all standard cleanliness parameters being followed and monitored by the approved expert clinical team.
- 5.2. The subjects must be very closely monitored during this procedure and for any AE/SAE.
- 5.3. For GTPs associated with modulating immune system such as CAR-T, given the high chance of CRS and other such life-threatening AEs, the clinical team should have appropriate mitigating treatments ready on standby.
- 5.4. All patient parameters during the infusion procedure must be recorded.

6. Post administration procedures and monitoring:

- 6.1. After the GTP administration is completed, the patients must remain in the hospital under close observation for at least the next 48-96 hours.
- 6.2. The disease, the GTP and the expected SAEs must be taken into account when determining the duration of close observation.
- 6.3. For CAR-T or immune modulating treatments, the close monitoring must include a battery of tests to predict or detect early, any possible SAEs. Appropriate mitigating measures must be kept ready on standby for immediate management of life-threatening AEs.
- 6.4. During the post GTP infusion period, all aspects of patient health must be recorded including serological, immunological, systemic parameters including biomarker tests if any.
- 6.5. All AEs and SAEs must be immediately informed to the EC and CDSCO.

7. Long Term Follow up: GTP studies require long term follow up to determine all direct and indirect effects of the genetic modification.

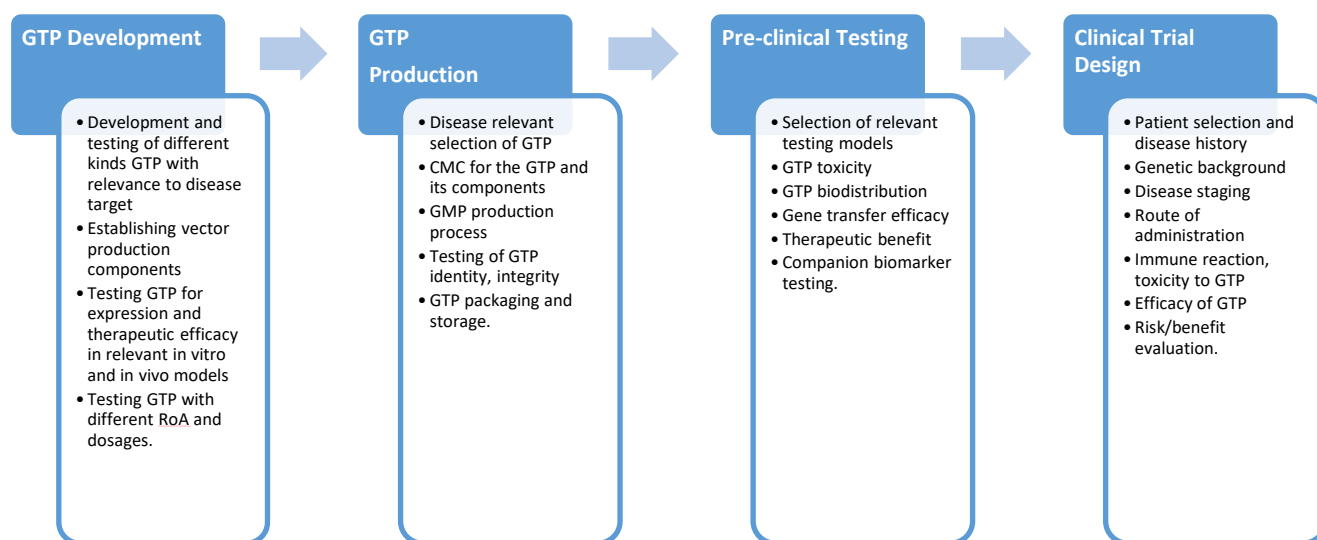
- 7.1. The trial investigator(s)/sponsors must ensure that the local sites have the required monitoring capability for regular follow ups, clinical, morphometric and biomarker testing.
- 7.2. There may be QoL questionnaires to be administered during this period to assess both the general health of the patient and the benefit of the GTP administration.
- 7.3. The clinical team must commit to all such procedures at the beginning of the trial and adhere to the approved protocols at all times during follow up.
- 7.4. The site team will also be responsible for reasonable efforts to follow up subjects who fail to comply with the previously explained procedures.

8. Patient data recording:

- 8.1. The trial investigator/sponsor is responsible for the accurate collection and safe storage of all trial associated data.
- 8.2. The data may be presented to requested by the local EC, CDSCO or GTEAC at various times during the trial duration.
- 8.3. All such data must be stored securely without being tampered or otherwise altered.

Schematic Representation of Steps Involved in GTP Development & Clinical Trial

(Brief points to consider. See full document for more details)



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