All studies involving the deliberate transfer of DNA, or DNA or RNA derived from recombinant DNA (human gene transfer) are subject to special submission, review, and reporting requirements at both the Federal and local levels. The overview of regulatory processes provided here summarizes [NIH](https://osp.od.nih.gov/biotechnology/faq-onthe-nih-review-process-for-human-gene-transfer-trials/) and [FDA](https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm) guidance on human gene transfer research.

**Regulatory Oversight and Institutional Review Requirements**

All human gene transfer studies must be submitted in the following order to:

1. National Institutes of Health (NIH); Office of Science Policy (OSP); (Food and Drug Administration (FDA)
2. UTHSCSA Institutional Biological Safety Committee (IBC)
3. UTHSCSA Institutional Review Board (IRB)

No subjects may be enrolled in gene transfer protocols until the NIH OSP review process has been completed, IBC and IRB approval have been obtained, and any other applicable regulatory authorization(s) have been secured.

**Federal Regulatory Oversight Requirements**

NIH Review

For investigator-initiated studies, the Principal Investigator (PI) is responsible for submitting the required documents (see Appendix M-I-A of the NIH guidelines) to the NIH OSP. For sponsor-initiated studies, the sponsor must complete the submission process and provide the local investigator with all information required for IBC and IRB review. In multi-center studies, the NIH OSP review process is the responsibility of the PI for the entire study.

After the documents are submitted, the NIH OSP will then provide a summary and copy of the submission to members of the Recombinant DNA Advisory Committee (RAC). As part of its initial review, RAC members assess whether the proposed study warrants public review and discussion at the RAC’s quarterly meetings open to the public.  Investigators or sponsors will be notified within 15 days of submission to OSP whether their study has been selected for public RAC review. After the RAC has completed its review process (including a public discussion, if necessary) a letter summarizing its comments and recommendations will be sent to the sponsor or PI, the FDA, and appropriate DHHS offices.  The RAC does not issue a formal approval for proposed studies; rather, its comments and recommendations are used to inform other review processes at the federal and local levels.

FDA Requirements

The FDA is responsible for the review and approval of gene therapy products as Investigational New Drugs (INDs). The study sponsor or PI for investigator-initiated studies will need to submit an IND application to the FDA. The IND number will be required for final IRB approval. See [FDA guidelines](http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm) for additional information on INDs and gene therapy studies.

|  |  |  |
| --- | --- | --- |
| **Required Reviews and Approvals** | NIH RAC # | Approval Date |
| FDA IND # | Approval Date |

|  |  |
| --- | --- |
| **Required Attachments** | **PI CV**  **Responses to Appendix M I – MVI submitted to NIH RAC** |

**Recombinant or Synthetic Nucleic Acid**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Gene Name | Gene Source(s)  (Genus, Species, Strain) | Function of Insert/Protein Expressed | Regulatory Elements in the Construct (i.e. promoters, enhancers, polyA, replication origins, terminators) |
| 1. |  |  |  |  |
| 2. |  |  |  |  |
| 3. |  |  |  |  |

|  |  |  |
| --- | --- | --- |
| **Vector Description** | **Vector Type** | **Plasmid**  **Viral**  **Naked DNA or RNA**  **Other:** Specify |
| **Vector Administration Route** | **IV**  **IM**  **IP**  **Other:** Specify |
| **Vector Source** | Genus, species N/A, not plasmid or viral |
| **Name of Vector** | Provide Technical Name  Provide reference or source OR N/A, not commercially available |
| **Vector Characteristics**  ***Check all that apply*** | **Replicating**  **Replication defective**  **Integrating**  **Oncolytic**  **Latency potential**  **Other:** Specify |
| **Host Target Cells** |  |
| **Type of Gene Transfer** | **In vivo**  **Ex vivo** |

|  |  |  |
| --- | --- | --- |
| **Biological Risk Assessment and Safety Precautions** | **Biological Safety Level**  ***Indicate the highest BSL applied in the experiment*** | **BSL 1**  **BSL 2**  **BSL 2+** |

**Location(s) and PPE**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Building name / Room number | Description of Work (Surgery, treatment, prep, patient care, other) | Patient Isolation | PPE  ***Check all that apply*** |
| 1. |  |  | **Standard**  **Contact**  **Droplet**  **Aerosol** | **single glove**  **double glove**  **surgical mask**  **respirators\***  **goggles/safety glasses**  **Face shield**  **lab coat**  **disposable lab coat/gown**  **Other:** |
| 2. |  |  | **Standard**  **Contact**  **Droplet**  **Aerosol** | **single glove  double glove**  **surgical mask**  **respirators\***  **goggles/safety glasses**  **Face shield**  **lab coat**  **disposable lab coat/gown**  **Other:** |

***\* The use of respirators requires medical evaluation and fit test prior to use.***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Specific Location Features** | **Will there be any additional specifications for work locations** | | **N/A**  **room ventilation**  **room signage**  **Other:** | | | |
| **Disinfectants** | Clinical areas will use the following disinfectants. | | | | [select all applicable]   * 10% solution household bleach * 70% ethanol * Other | | |
| If special disinfection procedures are required, explain. | | | | **N/A** | | |
| **Biohazardous Waste Management** | | The following types of biohazardous waste will be produced. | | [select all applicable]   * Sharps * Solid * Liquid * Pathological waste including infected or fixed animal carcasses * Other | | | |
| The biohazardous waste will be disposed of by the following method(s). | | [select all applicable]   * Regulated Medical Waste Box * Autoclaved Waste * Incineration * Inactivation (bleach to cultures) * Other | | | |
| **Spill Procedures** | | Emergency  Response & Spill  Plan posted in the clinical area? | | | | **Yes**  **No** | |
| **Exposure Prophylaxis and Public Health Considerations** | | Provide any safety instructions given to staff and/or family members during hospitalization and household contacts after subjects are discharged: | | | |  | |

***ICD template language***

***Instructions:*** For studies involving gene transfer, the FDA and UTHSCSA IRB have specific consent language requirements. Insert the language in this help sheet into your consent form under the specified headings. **This language is in addition to all other required language in the consent form template.** Further instructions are provided in *italics* throughout this document.

**PURPOSE:**

***Study Phase:******The purpose description should reflect the phase of the trial and should be based on pre-clinical and other clinical evidence.***

***Sample - Phase I – First in Humans***

This study is experimental. It is meant to investigate the safety, possible harms, and side effects of an experimental gene transfer agent called [X]. This is the first time that this gene transfer agent will be used in humans with your disease.

***Sample - Phase I – Dose Finding***

The investigator's goal is to find out the highest dose of the gene transfer agent that is safe. This is the first step in studying whether it can be used to treat others with your disease in the future.

***Sample - Phase II – Repeat Dosing***

The purpose of this study to find out if repeated doses of the gene transfer agent, [X,] are safe for research subjects with your disease, and to see if any side effects cause problems for subjects. This study is also being done to find out if giving [X] can help [name the disease] by [describe the mechanism of action].

***Sample - Phase III***

The purpose of this study is:

* To find out if subjects live any longer if the gene transfer agent is [state the delivery method of the gene transfer agent].
* To find out if the intervention [state the purpose of the intervention].

We will also continue to check the safety of the gene transfer agent.

***Describe the purpose of the gene transfer and the agent. Suggested wording (alter as necessary to describe this study):***

The gene transfer agent used in this study tries to provide corrected copies of one of your genes that does not function properly in your body [*can be used in studies supplying corrected genes for monogenic diseases, or the p53 gene for some cancers*].

Or-

The gene transfer agent used in this study tries to add copies of a gene that will alter the characteristics of the targeted cells [*for example, when inserting the HSV-TK gene into tumor cells to make them susceptible to destruction by ganciclovir*].

Or-

The gene transfer agent used in this study tries to add copies of a gene that increases the immune response against a tumor [*use, for example, when inserting the gene for IL-2 or interferon gamma*].

***Also include (when “genes” are mentioned)****:* Genes are the units of DNA--the chemical structure carrying your genetic information--that determine many human characteristics such as the color of your eyes, your height, and whether you are male or female.

***Vector description suggested wording:***

The gene transfer agent to be used in this study consists of:

* A virus called [*adenovirus, adeno-associated virus, retrovirus, other virus, i.e. fowlpox, vaccinia*], which has been changed in the laboratory so that it is not likely to reproduce or cause an infection once it is in your body.
  + ***A short description of each virus used in the vector should be added*, *such as:*** Adenovirus is a common virus found in human respiratory systems. In its normal state, it can reproduce and cause a respiratory infection. Respiratory illnesses caused by adenovirus infections range from the common cold to pneumonia, croup and bronchitis.
* Loops of DNA containing the gene [*naked plasmids*].
* Loops of DNA associated with fat molecules (called liposomes) that help improve gene delivery.

***Long-term follow-up of subjects is encouraged in gene transfer studies. There may be specific requirements for the duration of the follow-up period. See***

*https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm.*

Long-term follow-up in gene transfer research allows for the collection of important information on the long-term safety and effects of the gene transfer intervention used in this study. The long-term follow-up planned for this study will occur [frequency] for [length of time]. It includes [study-specific information, as available; e.g., drawing a small amount of blood once a year; completing a health history questionnaire every year; having a biopsy of the injection site every five years; etc.]. The investigators will try to make it easier for you to participate in long-term follow-up by [study-specific information as available, e.g., using mail and telephone to collect some information; arranging with your local doctor to collect blood or biopsy specimens and send them to investigators; etc.].

**PROCEDURES**:

***Dose Escalation Design (if applicable)****:* We do not know the highest dose of the gene transfer agent that is safe. To find out we will give the gene transfer agent to [number] subjects at one dose level. If that is safe we will raise the dose given to the next group of subjects. The dose you will get will depend on how many subjects get the agent before you and how they react. The investigator will tell you this information. This will help you think about possible harms and benefits. Since the gene transfer intervention is experimental, we don’t know what will happen at any dose level.

**RISKS AND DISCOMFORTS**:

***For Phase I studies****: Previous experiences with the same or similar vector, or even a different transgene, should be included in the risks section, particularly in phase I studies. Experience with animal studies may be relevant, as well as other human experience, and possibly even in vitro experience, when the meaning and limitations of the findings are carefully described. A general statement that humans and animals respond very differently and a statement about the relationship between the dose levels used in animals and humans would be appropriate. Uncertainty about the likelihood of the occurrence of most risks of harm from the gene transfer intervention at this early stage of research should be acknowledged.*

*Sample language for including risks obtained from animal studies:*

Humans and animals may respond to the gene transfer agent very differently. Side effects that occurred in animals may or may not occur in humans. Additionally, the amount of the vector that was used in animal studies was [*X*]-times the maximum dose that will be used in this study.

***For all Phase I studies state:***

The chance that you will experience any of the side effects listed is uncertain at this early stage of the research.

***For Phase II studies****: The consent form should include descriptions of risks of harm that were discovered in Phase I, such as reactions to the maximum-tolerated dose. It should be acknowledged that the extent of experience is still limited and that unanticipated harms may develop.*

***For Phase III studies****: The risk statement of a Phase III trial should reflect the results of earlier trials. It should also acknowledge that with a greater number of enrolled subjects, less-common side effects are likely to be recognized at this stage.*

***For all Phase III studies state:***

In this study there will be more people enrolled than in previous studies. Therefore we may learn of new side effects. If we do we will inform you of the additional possible side effects.

***Possible Cancer Risks Associated with a Study Agent***

*Sample1- For Viral Vectors:*

The vector, which carries the gene into your cells, is considered harmless in humans. However, it is possible that the vector could grow and/or make the cells cancerous. There is a risk that the vector may enter the normal tissue surrounding the tumor, or other sites in the body. Another risk is that the vector might stay in your body and cause cancer or other diseases. Your immune system is expected to reject (kill) the vector in [time amount]. Thus, the vector should not be able to survive and grow in your body. The risk of causing a new cancer is probably very small. Although some vectors have caused cancers, no cancers have yet been found in any of the experiments in which genes have been transferred into monkeys and humans using this vector.

*Sample 2- Pediatric Studies Using Retroviruses:*

Researchers have wondered whether a transferred gene might sometimes land in a place in a cell where it can cause harm. This happened to two children in another study. After getting the gene transfer, they developed leukemia (a type of blood cell cancer). A group of experts looked at all the test results. They found that gene transfer caused the leukemia by making some cells grow out of control. The children appear to be responding to treatment of the leukemia, but their long-term health is unknown at this time.

There is a risk of unknown size of your child developing cancer, such as leukemia, should you volunteer your child to enter into this experimental study. This is a serious risk because cancers of the blood can lead to death.

**Reproductive Risks**:

***For pregnancy/risk to fetus (For Women*):** One risk of this study is that the [gene transfer agent] could have harmful effects on a fetus. We do not know if the gene transfer you will get can become part of normal reproductive cells. If it can, it could cause harm to fetuses conceived after the gene transfer. If you are capable getting pregnant*,* you and your male partner(s) must use a method [*or two methods*] of birth control that work[*s*] well or you must not have sex. The investigator will talk to you about the types of birth control that are acceptable. You will have to do this the whole time you are in this study.

If you become pregnant during the research study, please tell the investigator and your doctor immediately. You also should not breastfeed during the study.

Also, we do not know if the [gene transfer agent] may be present in body fluids. If it is, it could be transmitted to sexual partners. Condoms are essential for preventing transmission to a sexual partner.

***For pregnancy/risk to fetus (For Men):*** One risk of this study is that the [gene transfer agent] could have harmful effects on a fetus. We do not know if the gene transfer you will get can become part of normal reproductive cells. If it can, it could cause harm to fetuses conceived after the gene transfer.

If you may want to have children in the future, we recommend that you bank sperm before beginning the study, so that you have sperm available that has no DNA from the vector and gene. The investigators will provide you with information on sperm banking at [study site].

In addition to sperm banking, fertile men are encouraged to use barrier birth control devices (i.e., condoms) with spermicide during sexual intercourse. You must do this the whole time you are in this study. The investigators will notify you when it is safe to stop barrier methods of birth control. If you have had a vasectomy, this [*is/is not*] an acceptable method of birth control. If a sexual partner becomes pregnant during the research study, please tell the investigator and your doctor immediately.

Also, we do not know if the [gene transfer agent] may be present in body fluids. If it is, it could be transmitted to sexual partners. Condoms are essential for preventing transmission to a sexual partner.

**CONFIDENTIALITY**:

***Because of the high degree of public interest in gene transfer research, the local or national media may seek information on or interviews with study subjects. State:***

The media (TV, newspapers, radio, Internet, etc.) may also want to know about this study. We will try our best to protect your privacy. However, because we have to share safety information, it is always possible that the media could find out who has been in the study.

**PARTICIPATION**:

***Potential subjects should be informed that at the time of their death, regardless of cause, an autopsy will be requested. State:***

Your investigator will ask your family for permission to perform an autopsy when you die, no matter what the cause. The evaluation of your organs after your death is a very valuable method to learn more about the good and bad effects of gene transfer. A "partial autopsy," in which needles are used to take samples of specific organs, may also be helpful. This type of autopsy does not require surgical incisions. You should talk about the possibility of autopsy with your family and health provider, and advise them of your wishes. The investigator may be able to tell you or your family what kind of autopsy information will be most helpful for this study. The study sponsor will pay all costs of the autopsy.