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WHITE PAPER

Biosafety in Clinical Research Sites.

By:

SABENA BLAKENEY, PHD, RBP

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Executive Summary

The National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (*NIH Guidelines*) provide oversight for the use of human gene transfer (HGT) products in human research participants under certain conditions.[1] The number of clinical trials involving HGT products has increased in recent years, and this trend is forecasted to continue as HGT products target cancers, infectious diseases, and rare diseases. Although academic research institutions are familiar with the *NIH Guidelines*, many clinical trial sites may need external help to become more familiar with the document and its requirements.

The *NIH Guidelines* provide a framework to address and minimize biosafety risks associated with HGT products, non-HGT products, and other biohazardous materials (e.g., human blood). The Guidelines detail safety and containment practices and procedures to protect clinical staff, patients, the community, and the environment against illnesses or other negative consequences from accidental exposures. Additionally, adhering to the *NIH Guidelines* facilitates the progression of research while promoting a safe working environment and site readiness for future HGT trials.

INTRODUCTION

In recent years, there has been an increase in clinical research sites participating in human clinical trials that use human gene transfer (HGT) products to treat diseases and other conditions. In addition to the US Food and Drug Administration (FDA), the use of HGT products is also regulated by the National Institutes of Health (NIH) within the Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (*NIH Guidelines*) under certain conditions.[1] However, research sites conducting clinical trials involving HGT products may not have experience with the *NIH Guidelines* and may not have the resources and knowledge to fulfill the requirements. As a result, clinical research sites may not recognize biological risks associated with the handling, storage, or disposal of HGT products. The lack of proper and adequate biosafety procedures and practices at clinical research sites using HGT or non-HGT products may result in any of the following:

- Increased risk of clinical staff, patients, community, and the environment to potential exposures
- Potential risk of cross-contamination of biohazardous materials
- Increased potential for occupational exposure to infectious pathogens
- Increased risk of injuries for clinical staff
- Potential delays in site initiation visits and clinical study startups

This white paper discusses the benefits of adopting biosafety standards, guidelines, and best practices in clinical research sites conducting HGT and non-HGT trials. Adherence to the *NIH Guidelines* facilitates safe research and promotes a safe work environment. The IBCs identify risks associated with biological materials and recommend mitigations to minimize exposure to HGT, non-HGT biologics, and other biohazardous materials, which protects clinical staff, patients, the community, and the environment. Additionally, the IBCs can assist in developing and implementing safe and best biosafety practices at the clinical research sites to promote site readiness for IBC approval of future HGT studies. Organizations should choose to conform to the *NIH Guidelines* for non-HGT biologics or other biohazardous materials to demonstrate their commitment to protecting workers, patients, and the community, as well as facilitating cutting-edge research in a safe environment.

BACKGROUND

Recent advances in gene therapy research resulted in a rise in gene therapy products developed and tested in human clinical trials (Figure 1).[2] Furthermore, the application of mRNA-based technology for COVID-19 vaccines accelerated the use of HGT products to treat diseases and improve human health.

What is HGT?

HGT refers to modifying one's genes or using genetic materials to treat, cure or prevent disease. HGT includes changing faulty genetic material or replacing it using a vehicle (i.e., viral vector) to deliver the suitable genetic material into the human body. Another HGT approach facilitates modifications outside the body by removing cells from a patient, modifying them, and returning the modified cells to the patient as a treatment.

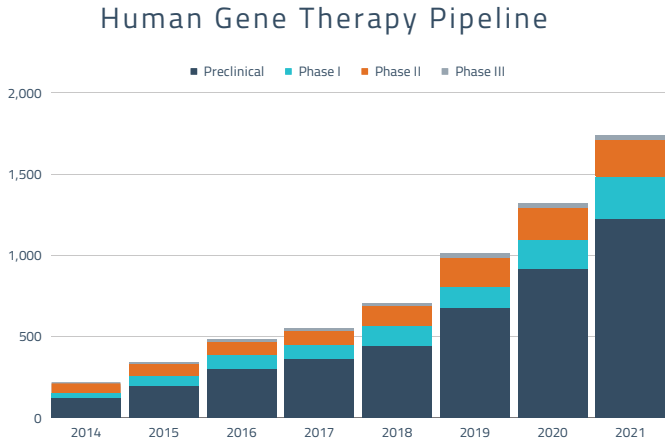

Figure 1: HGT Pipeline in the Human Clinical Trial Phases. Data adapted from the ASGT Pharma Intelligence Quarterly Report [2]

To date, there have been 18 HGT products approved by the FDA. These include eight (8) HGT products against cancers, six (6) HGT vaccines against infectious diseases, and four gene therapies against rare diseases.[3,4] Additionally, a search using the term "gene therapy" on ClinicalTrials.gov resulted in more than 1200 HGT studies actively recruiting patients.

Oversight of HGT Products

The FDA Center for Biologics Evaluation and Research (CBER) regulates HGT products. The FDA has published several guidance documents to evaluate the safety and efficacy of HGT products to assist with submitting the investigational new drug (IND) applications to initiate human clinical trials in the US.

If support for developing an HGT product is through NIH funding, then the product falls under the oversight of the *NIH Guidelines*. The *NIH Guidelines* require an Institutional Biosafety Committee (IBC) to review the handling and disposal of HGT products before their use with human research participants. The IBC functions as a local oversight body of the clinical site and must have a registration with the NIH Office of Science Policy (OSP) before convening and reviewing HGT studies. When not subjected to the *NIH Guidelines*, sites often conform to the document and use IBCs to promote safe and responsible research.

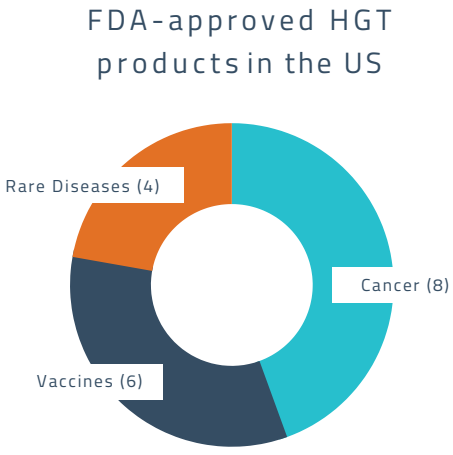

Figure 2: HGT products approved gy the FDA

The Role of IBCs in Clinical Studies

The IBCs are essential in overseeing HGT products used in clinical trials. Data shows that as the number of HGT IND applications increased over time, the number of registered IBCs followed a similar trend over the same period.[4] Additionally, the number of registered IBCs more than doubled between 2019 and 2022, including more than a 400% increase in externally administered IBCs. The externally administered IBCs, which usually support clinical research sites, have increased to surpass self-administered, local IBCs in less than four years (Figure 3).[4,5]

The primary focus of the IBC is to ensure that clinical studies involving HGT products are performed safely and responsibly while protecting clinical staff, patients, the community, and the environment from potential exposures to HGT products. The IBC assesses the risks posed by the HGT products and ensures that mitigation measures are in place against the identified risks for safe clinical research.

BIOSAFETY AT CLINICAL RESEARCH SITES

Biosafety refers to the safe handling and containment of infectious microorganisms and hazardous biological materials using facility design and safeguards, administrative policies, personal protective equipment (PPE), training, work practices, and safety equipment to prevent exposure of biohazardous materials to workers, the community, and the environment.[6]

The lack of proper and adequate biosafety practices and procedures in conducting clinical trials using HGT and non-HGT biologics at clinical research sites may result in any of the following:

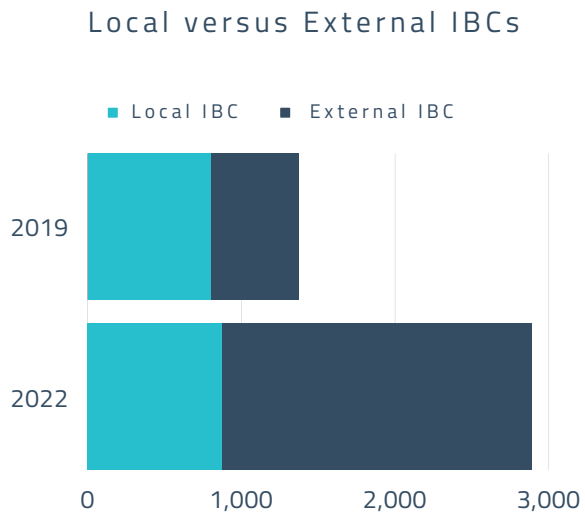

Figure 3: NIH-registered External vs Local IBCs

- Increased risk of clinical staff, patients, community, and the environment to accidental exposures to HGT and non-HGT biologics
- Potential risk of cross-contamination of HGT, non-HGT biologics, and other biohazardous materials (e.g., human clinical samples)
- Increased risk of occupational exposures to bloodborne pathogens (BBP)
- Increased risk of needlestick injuries for clinical staff
- Delay in site initiation visits and clinical study startups Inhibit the progression of safe research
- Unsafe working environment for staff and patients

Adherence to the *NIH Guidelines* by using IBCs to review studies, decreases the risk of accidental exposures to clinical staff, patients, the community, and the environment. Clinical research sites should leverage the Occupational Health and Safety Administration (OSHA) BBP Standard, existing infection control, and waste handling procedures to conform to the *NIH Guidelines*. The IBCs also use guidelines and best practices in the Biosafety in Microbiological and Biomedical Laboratories (BMBL), 6th edition, as well as the components of the OSHA BBP standard (e.g., standard precautions) to promote a safe working environment, facilitate safe research, and promote site readiness for future HGT trials. While not a requirement, clinical research sites should adopt policies to conform to the *NIH Guidelines* for non-HGT studies and other biohazardous materials (e.g., blood, body fluids) to bolster a safe working environment and protect staff, patients, and the community against biohazards.

Protecting the Research Community Against Biosafety Risks

IBCs perform risk assessments to identify biosafety hazards in research settings. For example, most HGT products use viral vectors derived from adeno-associated viruses, lentiviruses, adenoviruses, retroviruses, herpes simplex viruses, and poxviruses.[2] Clinical research sites may not have adequate expertise in viral vectors to assess risks properly (e.g., immunogenicity, shedding, insertional mutagenesis, germline transmission). IBCs can provide the expertise necessary to evaluate risks associated with viral vectors to minimize the risk of occupational exposures. The IBCs can also recommend proper disposal of bandages and materials following HGT administration to protect the community and the environment from HGT exposure.

Similarly, clinical research sites may need to become more familiar with biosafety cabinets (BSCs) used to prepare the HGT or non-HGT biologics as they offer personnel protection against aerosol hazards. The IBC recommends against the use of a laminar flow hood for biohazardous materials, including HGT and non-HGT biologics, to protect clinical staff from accidental exposure. Additionally, the IBCs ensure that correct PPE is used during work activities and verify that PPE is disposed of as biohazardous waste before leaving the area to prevent contamination and potential exposure to other clinical personnel in shared spaces, such as hallways.

The IBCs review facility arrangements and existing policies, procedures, and practices to determine if biohazards are adequately managed. Site review by the IBC includes:

- Storage locations for biologics, including HGT products
- Preparation and patient dosing rooms
- Disinfectant effectiveness against biohazardous materials
- Waste disposal procedures
- Emergency and spill response procedures
- Good Microbiological practices and procedures
- Safe sharps practices
- Proper PPE use and disposal

Biosafety Controls

Figure 4: Types of Biosafety controls and common examples from a clinical research site

If necessary, IBCs recommend biosafety controls to minimize risks during the clinical trials by using engineering and administrative controls, standard operating procedures (SOPs), and PPE (Figure 4).[1,6]

Therefore, IBCs are essential in identifying and mitigating biosafety risks associated with clinical trials to protect clinical staff, patients, the community, and the environment by minimizing potential risks from HGT, non-HGT biologics, and other biohazardous materials.

Promoting Site Readiness for Future HGT Trials

Clinical research sites not working with HGT should consider conforming with the *NIH Guidelines* as best practice to protect clinical staff and the community against accidental exposures to biologics. The sites can use IBCs to identify general risks associated with storing, handling, and disposal of non-HGT products or other biohazardous materials. The IBCs can also serve as a resource to develop and implement biosafety policies, procedures, and practices to prepare workplaces for future HGT studies. The number of sites working with HGT and requiring IBCs is increasing exponentially, and being prepared is a good investment in future needs. If the site is selected for an HGT trial, it will be able to convene the established IBCs quickly to review the new research and update existing procedures to protect clinical staff and the community. This preparation will decrease the startup time significantly for new HGT studies.

CONCLUSIONS

In a 2019 FDA statement, Dr. Scott Gottlieb, the FDA Commissioner at the time, predicted that the "FDA will be approving 10-20 cell and gene therapy products a year based on the current pipeline and clinical success rates of these products."[7] However, the HGT products must undergo rigorous clinical trials before the FDA approves them. Using IBCs at clinical research sites assists with biosafety compliance and conformity to promote a safe work environment and protect clinical staff, patients, and the community against accidental exposures to HGT products used during the trials. The IBCs also aid in identifying and implementing good biosafety procedures and practices to prepare the clinical research sites for future HGT clinical trials. Additionally, conforming to the *NIH Guidelines* for non-HGT studies facilitates safe research with a safe work environment to protect clinical staff and the community against illnesses and other negative consequences due to exposure to biohazardous materials.

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3121 Ponce de Leon Blvd, Coral Gables FL 33134