Gene Therapy
DNA vaccines
CAR-T
CRISPR/ Gene editing
mRNA therapeutics

Ethical and Biosafety Oversight of Gene Transfer Clinical Research:

What Sponsors and CROs Need to Know?

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SUMMARY

- **All human gene transfer clinical trials inside or outside the USA, if subject to the *NIH Guidelines*, require approval by an Institutional Biosafety Committee (IBC).**
- **Each clinical trial site must have its own IBC registration.**
- **April 2019 changes to the *NIH Guidelines* significantly altered federal oversight of gene transfer clinical research.**
- **IRBs and the IBCs have separate, complimentary oversight responsibilities.**
- **Planning for IBC oversight is a critical and often neglected initiation step for gene transfer clinical research.**
- **Sponsors and CROs should seek expert advice on IBC oversight at an early stage of clinical trial planning.**

INTRODUCTION

The number of drug products under development that incorporate recombinant or synthetic DNA or RNA, viral vectors, and/or genetically-modified organisms (“GMOs”) continues to grow rapidly, and several such products have received marketing approval from the FDA. This paper focuses on important points to consider when planning to initiate clinical trials with these products at sites inside or outside the USA, if the research is subject to rules and regulations of the FDA and/or the National Institutes of Health (NIH) of the United States. In particular, we focus on the roles of Institutional Biosafety Committees (IBCs) and Institutional Review Boards (IRBs) in approving and facilitating study startup.

Broadly speaking, IRBs are tasked with protecting the rights of research participants in clinical trials. IBCs are tasked with mitigating risks posed by gene transfer research to clinical staff, public health, and the environment. With proper planning, IRBs and IBCs can work together to ensure safe, efficient, and compliant site initiation.

IRB OVERSIGHT & IBC OVERSIGHT COMPARISON

IRB Oversight	IBC Oversight
• Mandated by federal law (per 21 CFR 50 and 56) and international agreements	• Mandated by the *NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules (NIH Guidelines)*
• Primarily focused on the study participant - Assessment of risks and benefits - Informed consent - Privacy and confidentiality	• Primarily focused on public health and environment - Risk to laboratory and clinical staff - Risk to public health - Risk to environment
• Guiding principles - *Belmont Report* - *Common Rule* - *Declaration of Helsinki* - *Nuremberg Code*	• Guiding principles - *NIH Guidelines* - Biosafety in Microbiological and Biomedical Laboratories (BMBL–published by CDC and NIH) - WHO | *Laboratory Biosafety Manual* - Peer-reviewed publications in biosafety and microbiology

This paper covers selected rules and regulations found in Title 21 of the United States Code of Federal Regulations (for FDA and IRB oversight) and in the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*, for NIH and IBC oversight). This paper does not address requirements of the European Medicines Agency (EMA) or other regulatory authorities outside the USA.

FDA AND NIH OVERSIGHT

For the purposes of drug development, the FDA does not use a separate regulatory category for GMOs or gene transfer products. Any product whose primary mechanism of action (PMOA) involves genetic modification will almost certainly be regarded as a biologic product regulated by the Center for Biologics Evaluation and Research (CBER). Gene therapy products and cancer vaccines are reviewed by the CBER Office of Tissues and Advanced Therapies (OTAT, formerly known as the Office of Cellular, Tissue and Gene Therapies, or OCTGT). Genetically modified vaccines other than cancer vaccines are reviewed by the CBER Office of Vaccines Research and Review (OVRR). The formal process to bring these products to market is the same as for any biologic, requiring an Investigational New Drug (IND) application for clinical research and a Biologic License Application (BLA) for marketing approval. Combination products incorporating genetically modified components are assigned to a Center (CBER, CDER, or CDRH) depending on the PMOA.

Any clinical trial in the USA involving these products will require approval by an IRB.

In contrast to FDA classification, which primarily depends on the PMOA and indication, the NIH categorizes genetically modified products according to the technology used to produce them. These rules are spelled out in the *NIH Guidelines*. Specifically, *NIH Guidelines* Section III-C-1 provides a definition of **Human Gene Transfer (HGT)** research[1]: HGT research is the deliberate transfer into human research participants of recombinant or synthetic nucleic acid molecules, with certain exceptions such as research with products incorporating only small or inert nucleic acid molecules, or for single-patient expanded access research. In practice, this means that **most investigational products that contain genetically modified or synthesized DNA or RNA are HGT products**. Exceptions include small, transient molecules such as most short, interfering RNA (siRNAs) and antisense oligonucleotides (ASOs). Exceptions may also include gene editing approaches that delete chromosomal sequences without adding any exogenous genetic information. Almost any product that incorporates a "viral vector" will be considered an HGT product. Sponsors and CROs should consult a biosafety professional or a molecular biologist to determine whether a particular investigational product meets the NIH definition of HGT product. Inquiries of this type may also be directed to the NIH Office of Science Policy.[2]

EXAMPLES OF INVESTIGATIONAL CELLULAR THERAPY FOR CANCER: IS IT HUMAN GENE TRANSFER (HGT)?

1. T cells expressing synthetic Chimeric Antigen Receptor (CAR-T cells): Yes, it is HGT.
2. Biopsy T cells isolated as Tumor Infiltrating Lymphocytes (TILs) and expanded without genetic modification prior to infusion: No, it is not HGT.
3. T cells transduced with T Cell Receptor (TCR) genes cloned from TILs prior to infusion: Yes, it is HGT.

The definition of HGT research is extremely important to understand because **any HGT clinical trial inside or (in many cases) outside the USA, if subject to the NIH Guidelines, must have IBC approval prior to initiation.** Clinical research is subject to the *NIH Guidelines* if any of the following apply: i) the clinical trial site receives relevant NIH funding; ii) the investigational product was developed with NIH funding; iii) the clinical trial sponsor receives relevant NIH funding; iv) voluntary compliance is chosen per best practices recommended by the *NIH Guidelines.*

APRIL 2019 AMENDMENTS TO THE NIH GUIDELINES

Over the first 40 years that the *NIH Guidelines* were in effect, the Guidelines required that each HGT protocol be reviewed, or considered for review, by an NIH committee known as the Recombinant DNA Advisory Committee (RAC). An important component of RAC review was responses to "Points to Consider" as specified in Appendix M of The Guidelines. Prior to April 2019, Appendix M also mandated a number of reporting and registration requirements for sponsors and investigators engaged in HGT research. In September 2018, the NIH Director announced that RAC review and Appendix M reporting requirements were rescinded pending final action on a series of proposed changes to the *NIH Guidelines*. **In April 2019, a final action was announced, whereby the RAC was permanently dissolved and the previous Appendix M was permanently deleted from the *NIH Guidelines*.**[3]

Under these changes, the NIH will no longer solicit or accept any reports or registrations previously mandated under Appendix M. The April 2019 amendments also made several other changes affecting HGT research.

For example, it is now recommended that IBCs reduce or eliminate consideration of study subject safety (as this is an IRB responsibility).

HIGHLIGHTS OF APRIL 2019 CHANGES TO THE NIH GUIDELINES AFFECTING HUMAN GENE TRANSFER RESEARCH:

1. IBC approval is still required at every clinical trial site
2. The former Recombinant DNA Advisory Committee (RAC) is dissolved. A new committee, NExTRAC, is tasked with some of the same advisory roles as the previous RAC but does not have any role in routine review of clinical trials.
3. The former Appendix M is deleted in its entirety. All previous Appendix M reporting requirements are rescinded.
4. IBCs are no longer required to review informed consent or adverse event reports.
5. Single subject expanded access INDs and protocols are exempt from IBC review.

IBC REVIEW OF CLINICAL TRIALS

The *NIH Guidelines* specify that each clinical trial site must have its own IBC registration (which is why there are well over 1,000 IBCs registered in the NIH IBC-RMS system). IBC membership must include scientific experts qualified to evaluate the research under study, and also must include two community representative members who live near the clinical trial site and are not affiliated with the clinical trial site. Clinics and hospitals frequently lack the scientific and regulatory expertise to independently register and maintain an IBC. Even IBCs administered by major academic medical centers can struggle to find the time and attention required to adequately review gene transfer research. Therefore, many sponsors, CROs, clinics, hospitals, and universities find that it is beneficial to partner with an IBC service provider to staff and administer an IBC on behalf of each clinical trial site.

The *NIH Guidelines* require that each clinical trial protocol be approved by the respective IBC at each clinical trial site prior to initiation of research under that protocol. Each site must have its own IBC; thus, for a twenty-site clinical trial using a product developed with NIH funding, there must be twenty unique IBC registrations. IBC approval must issue from a convened public meeting of the IBC. IBCs may convene in person (face-to face) or over the internet. IBCs must assess and deliberate on the suitability of the site and the investigator for safe conduct of the proposed research. After IBC approval, the *NIH Guidelines* require continuing IBC oversight for

as long as dosing occurs. Changes in research require prior IBC approval, and unexpected events such as loss of containment or lab-acquired illness must be promptly reported to the IBC.

WHAT DO IBCs REVIEW? EXAMPLES OF IMPORTANT QUESTIONS FOR IBC CONSIDERATION:

1. Does the principal investigator have appropriate qualifications?
2. Do site personnel have the necessary training?
3. Is the proposed biosafety level appropriate for the study?
4. Does the proposed procedure include appropriate personal protective equipment?
5. Are items such as biological safety cabinets and eye wash stations properly maintained?
6. Is there a good plan in place for handling needles and sharps disposal?
7. Does the proposed gene transfer product pose a threat to public health or the environment?

IRB REVIEW OF GENE TRANSFER RESEARCH

In many aspects, IRB review of gene transfer research addresses all of the same questions as IRB review of any clinical trial, especially with regard to the general concerns of risk/benefit assessment and informed consent. However, some gene transfer studies do pose unique challenges that not all IRBs may be prepared to address. For example, certain classes of gene transfer agents are known to pose a risk of creating cancer causing chromosomal abnormalities through insertional oncogenesis. As another example, experimental treatment with a first-generation version of a gene transfer vector may induce an immune response that precludes future treatment with subsequent more advanced versions of the product. Proper risk benefit assessments in these cases requires that IRBs include members with sufficient understanding of the molecular and immunological issues involved. Reviewing informed consent and recruitment materials to address the complex nature of gene transfer research is also a special challenge for IRBs.

Under older *NIH Guidelines* processes, IRBs sometimes took comfort—rightly or wrongly—in the fact that each protocol was subjected to RAC review and IBC review of informed consent and subject safety considerations. Under the latest changes, RAC review is eliminated, and IBCs are no longer required to consider subject safety as part of the IBC approval process. This means that IRBs must be prepared to accept primary responsibility for ensuring proper technical and ethical review of gene transfer protocols. Because IBCs necessarily include members with advanced technical understanding of molecular methods, an ideal solution is a system whereby the IBC and IRB work together to provide nefficient and comprehensive oversight.

CONCLUSIONS: PLAN AHEAD AND SEEK EXPERT ADVICE

Sponsors and CROs planning Phase 1, 2, 3, or 4 clinical trials or multi-patient expanded access protocols should keep in mind that review of HGT research by the FDA and the IRB are necessary but not sufficient. Requirements for IBC review should be included in project planning at the earliest possible stage while considering product handling, investigator qualifications, and site selection. Proper planning and coordination with gene transfer experts can ensure safe, compliant, and efficient site initiation and clinical trial startup and execution.

ABOUT THE AUTHOR

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ABOUT WCG IBC

Since 2001, WCG has been the unrivaled leader in IBC administration. Since then WCG IBC has expanded our network of more than 900 global institutions, reviewed more than 800 protocols since 2020, and reviewed over 3,500 protocols since 2020. Our highly-experienced IBC board members include experts from biosafety and infection control, local unaffiliated members, and representatives from study sites, with a combined 200+ years of experience.

REFERENCES

[1]Section III-C-1. Experiments Involving the Deliberate Transfer of Recombinant or Synthetic Nucleic Acid Molecules, or DNA or RNA Derived from Recombinant or Synthetic Nucleic Acid Molecules, into One or More Human Research Participants.

Human gene transfer is the deliberate transfer into human research participants of either:

1. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or
2. Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules, that meet any one of the following criteria:
    a. Contain more than 100 nucleotides; or
    b. Possess biological properties that enable integration into the genome (e.g., cis elements involved in integration); or
    c. Have the potential to replicate in a cell; or
    d. Can be translated or transcribed.

Research cannot be initiated until Institutional Biosafety Committee and all other applicable institutional and regulatory authorization(s) and approvals have been obtained.

The deliberate transfer of recombinant or synthetic nucleic acids into one human research participant, conducted under an FDA regulated individual patient expanded access IND or protocol, including for emergency use, is not research subject to the *NIH Guidelines* and thus does not need to be submitted to an IBC for review and approval.

[2]Questions may be addressed to **NIHGuidelines@od.nih.gov**

[3]https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-modernizing-human-gene-therapyoversight

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