



NIH OHSRP Education Series

# Considerations for Informed Consent in Gene Therapy Trials

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# Disclosure



I am an employee of WCG, a provider of IRB and IBC Services.

I have no other actual or potential conflict of interest in relation to this presentation.

# Agenda



- Defining gene therapy and gene transfer research
- NIH and FDA guidance for informed consent
- Current best practices for IRBs and IBCs to work together on ICF review
- Major categories of risk associated with cell and gene therapy clinical research
- Patient perspectives
- Continuing challenges

# Informed Consent- General Requirements for Any Trial



## To be included in ICDs

1. Description of the research
2. Description of risks
3. Description of benefits
4. Alternatives to participation
5. Explanation of confidentiality
6. Explanation of compensation for injuries
7. Whom to contact about the research
8. Explanation that participation is voluntary
9. Statement regarding collection of identifiable private information or identifiable biospecimens

# Informed Consent in Gene Transfer - Considerations



## Should always be included

Explanation that product contains genetically modified DNA or RNA (or is capable of modifying subjects DNA or RNA).

## May be included, where appropriate to the research under review.

- Insertional Oncogenesis
- Reproductive Risk
- Vector-related Effects
- Transgene-related Effects
- On-target And Off-target Immune / Inflammatory Effects
- Long Term Follow-up
- Potential Need For Autopsy
- Potential Media Attention
- Other Potential Risks Of New Technologies



# Human Gene Transfer Technology

A very brief overview

# Gene Transfer Alters the Flow of Information in the Cell



Central paradigm of information transfer in molecular biology



# Gene Transfer Defined In *NIH Guidelines*



## **Human Gene Transfer (HGT) research is defined in Section III-C of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*.**

- In general, HGT research involves administration to a human subject of products that contain genetically modified DNA or RNA- with certain exceptions.
- HGT research subject to *NIH Guidelines* must be approved by an Institutional Biosafety Committee (IBC) registered with the NIH.
- FDA has approved/authorized HGT products including:
  - Vectored gene therapies for inherited disease
  - *Ex vivo* engineered cellular therapies for cancer and inherited disease
  - Oncolytic viruses
  - mRNA and viral vector vaccines for COVID-19 and other infectious diseases.



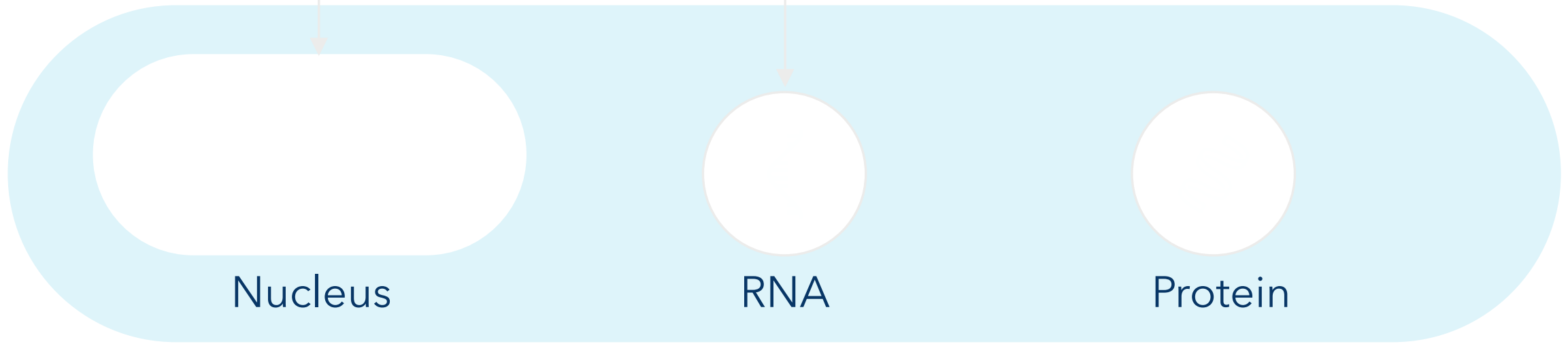
# Per Current Definition, Gene Transfer Products Add or Modified DNA or RNA to a Cell



DNA Vector



RNA Vector



Nucleus

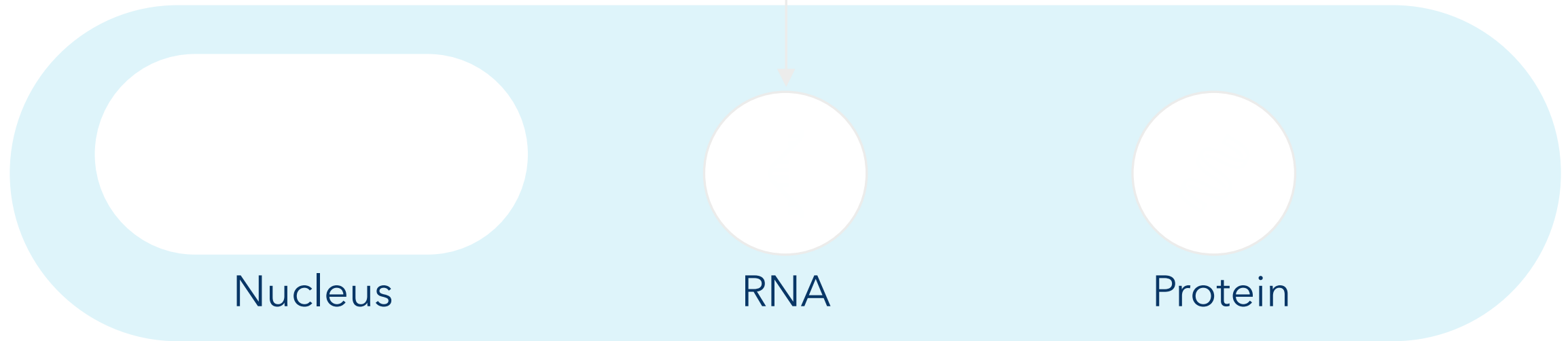
RNA

Protein

# mRNA products usually introduce transient changes to the genetic information content of a cell



RNA Vector

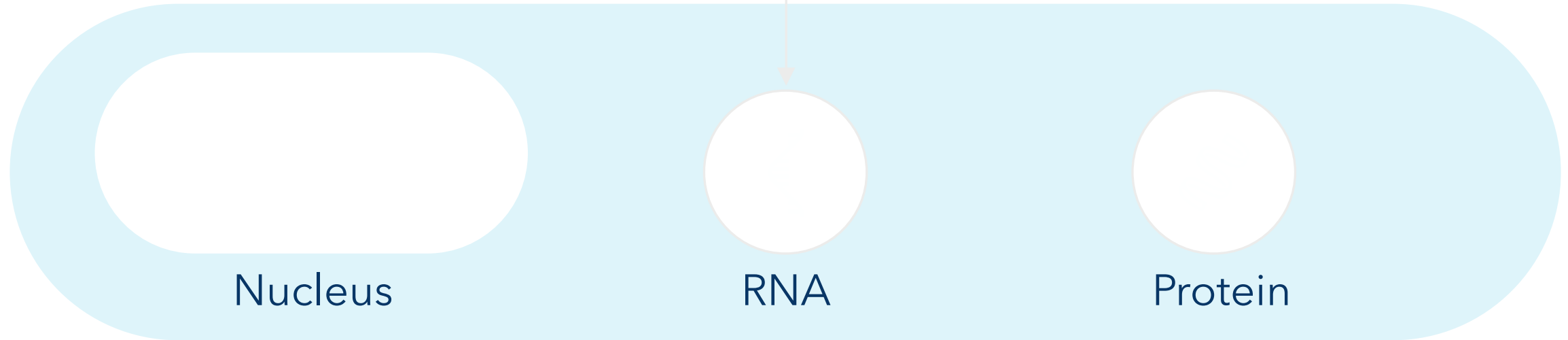


**mRNA products usually introduce transient changes to the genetic information content of a cell**

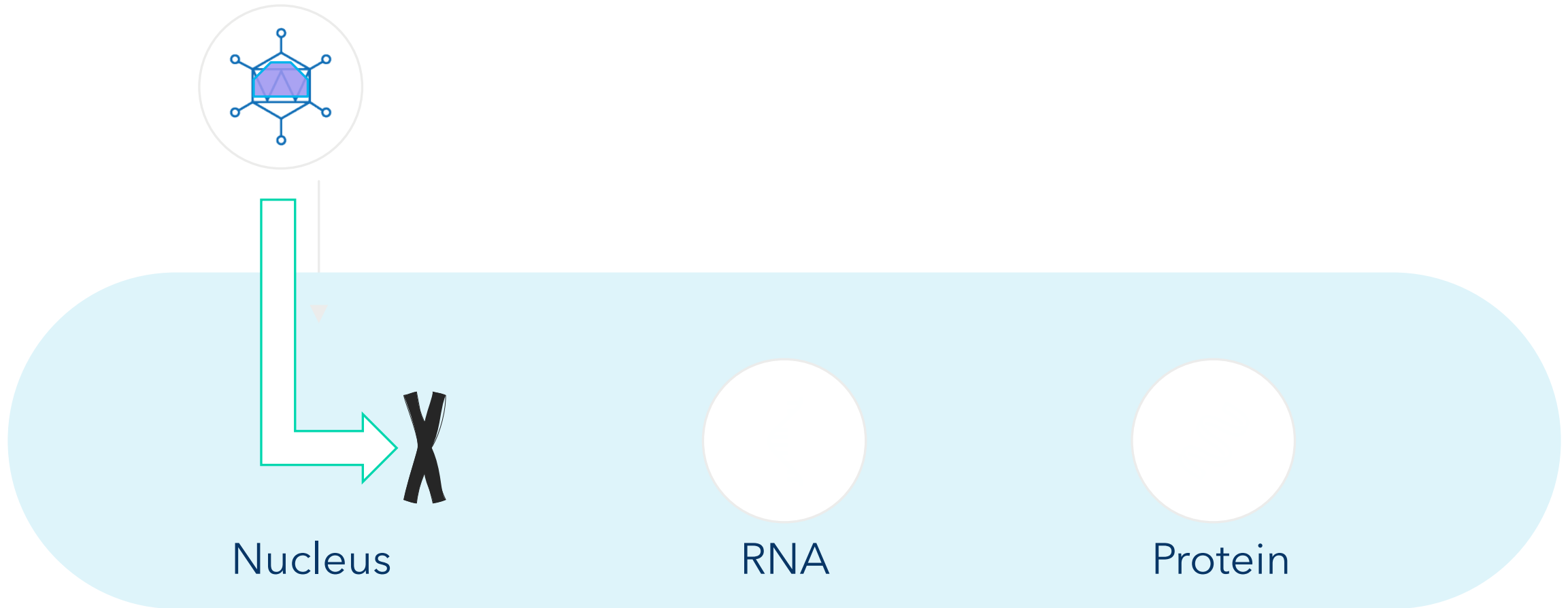
**Some of these are classified as "Gene Therapy"**



RNA Vector



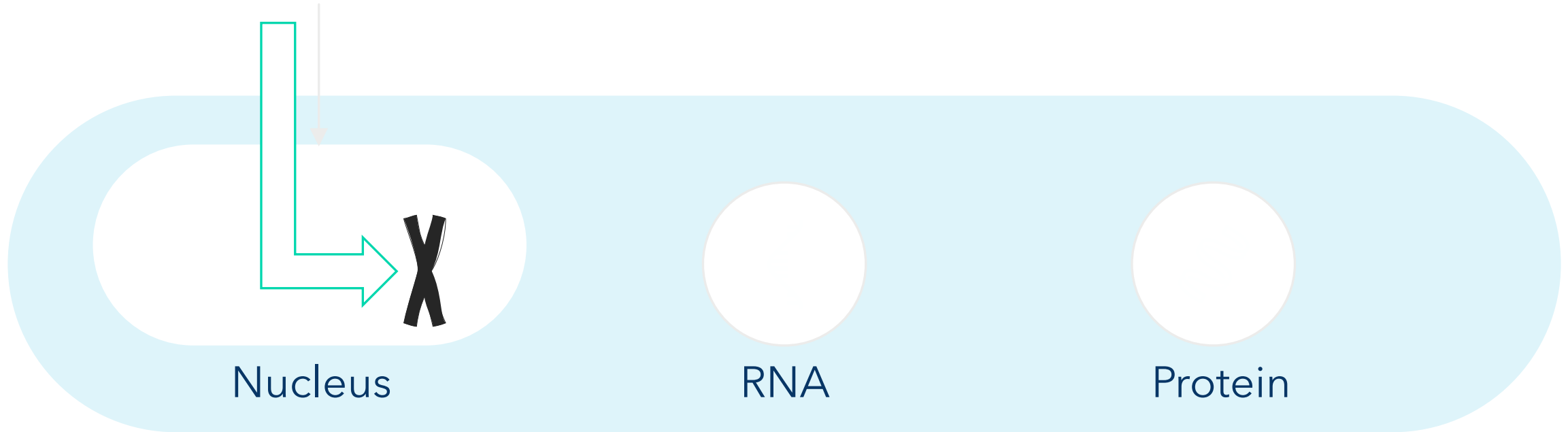
# Some (not all) gene therapies permanently insert engineered DNA into the chromosome



# Some (not all) gene therapies permanently insert engineered DNA into the chromosome

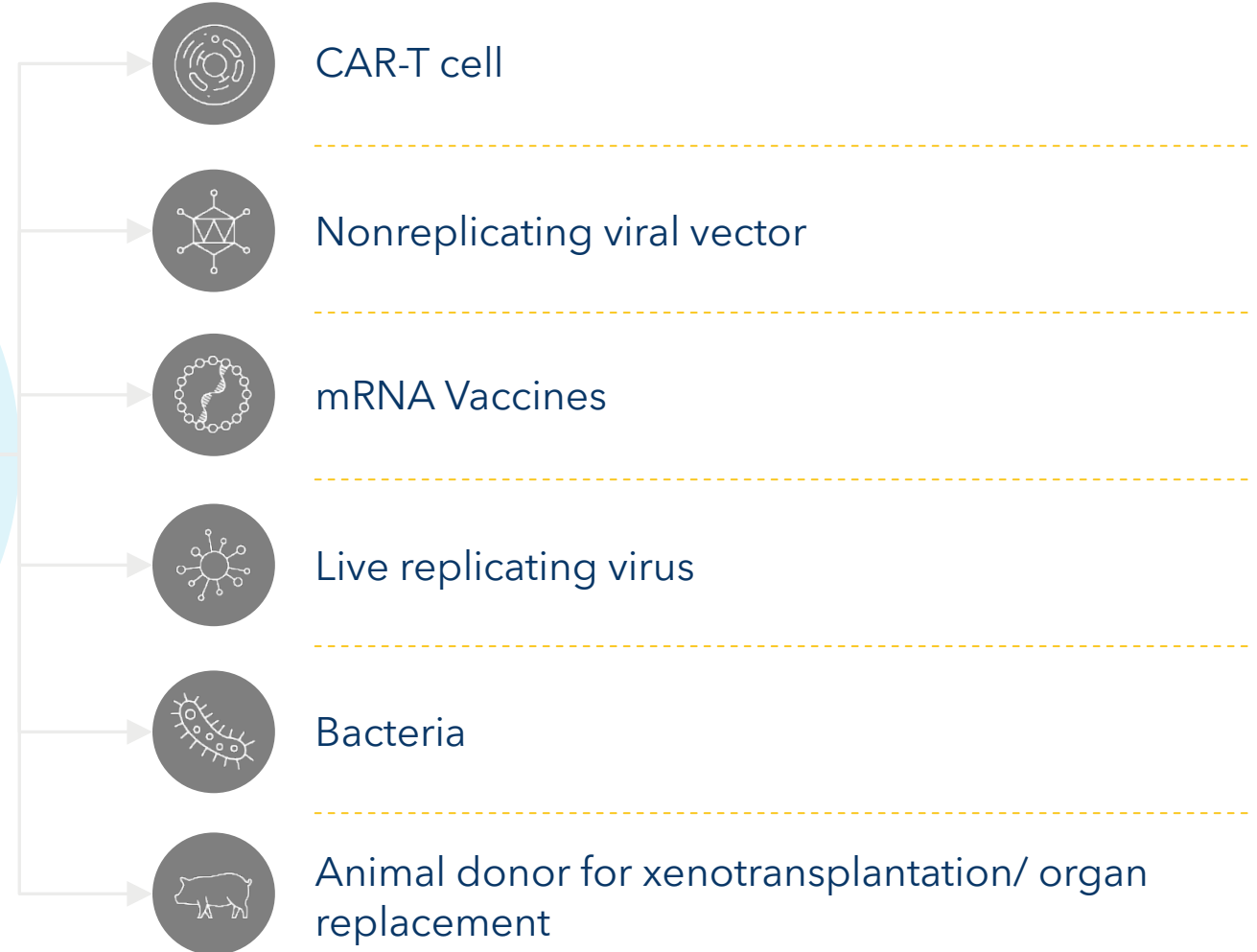


Some vectors, including those derived from retro/lentiviruses and transposons, provide DNA that is **integrated** into the chromosome.



# IBC approval is required for most clinical trials involving gene transfer

Engineered  
DNA / RNA



# Two pathways of gene therapy delivery

## In Vivo gene delivery



Lipid nanoparticle contains mRNA to induce vaccine response or provide transient gene replacement



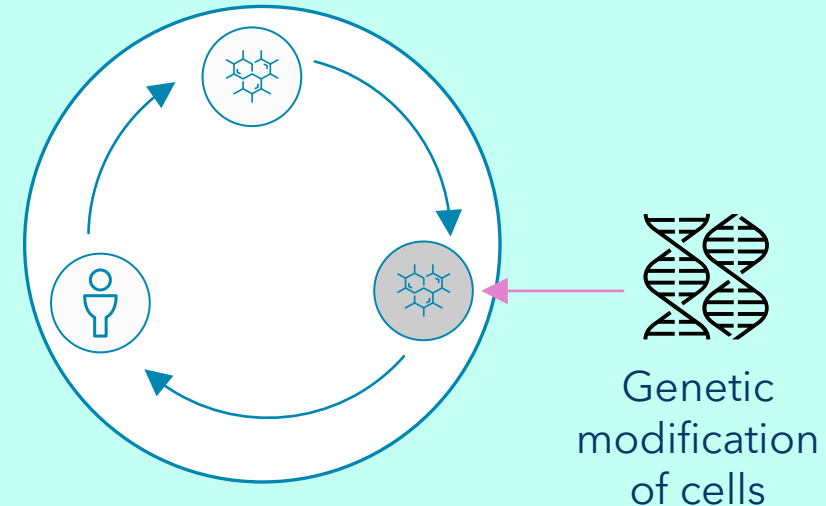
Nonreplicating viral vector delivers functional gene to treat inherited disease.



Replicating oncolytic virus selectively kills cancer cells.

## Ex Vivo gene delivery

Remove cells from participant



Return genetically-modified cells to participant



# **Institutional Review of Informed Consent in Human Gene Transfer Research**



# Informed Consent for CGT - Changing Roles for IRB and IBC



- **Prior to 2016**
  - The NIH required IBC to review ICF, and published a list of points to consider.
  - All HGT protocols were reviewed by RAC (NIH Recombinant DNA Advisory Committee).
  - Appendix M required IBC review of SAE and safety reports.
- **Between 2016 and 2018**
  - NIH required IBC to review ICF, but rescinded the list of points to consider.
  - Very few protocols were reviewed by RAC.
  - Appendix M required IBC review of SAE and participant safety reports.
- **After 2019**
  - IBC review of ICF no longer required by NIH (remains optional).
  - Primary responsibility for participant safety review shifted to IRB.
  - Previous Appendix M deleted.
  - Participant safety review by IBC discontinued.
  - RAC renamed and repurposed; no longer routinely reviews clinical protocols.

# Minimal Review Requirements Since 2019



## IRB Review

Required for all nonexempt clinical trials.

IRB focus is **study participants**.

- Risk
- Benefit
- Consent
- etc.

## IBC Review

Required for clinical trials subject to *NIH Guidelines*.

IBC focus is **staff, public** and the **environment**.

- Containment
- Disinfection
- Disposal
- Accidental exposures
- etc.

# IRBs and IBCs Working Together



- IRBs may or may not have expert members familiar with genetic engineering and molecular biology.
- IBCs often have members with a strong interest in human subject protection and bioethics.

## To promote collaboration:

- Institutions can request IBC review of ICF and subject-facing documents.
- IRBs can request a consult from the IBC.
- IRB representatives can attend IBC meetings (which are normally public meetings).
- IRB and IBC may hold joint seminars and journal clubs to share knowledge on new technology and publications.

# Informed Consent for CGT - Previous Guidance from NIH



Previous NIH Guidance included specific points to consider for gene transfer ICF, including:

1. Genetically modified nature of investigational product.
2. Long term follow-up.
3. Reproductive considerations.
4. Request for autopsy.
5. Interest of the media and others.

These points can still serve as a guideposts in ICD review.

## Long Term Follow-Up After Administration of Human Gene Therapy Products Guidance for Industry

January 2020

- Requirement for and duration of LTFU depends on nature of the product.
- Specifically dependent on expected potential risk of delayed adverse events associated with the IP.
- 15-year LTFU is often recommended depending on expected risks.
- Delayed adverse events are a particular concern for gene transfer agents that modify the chromosome.
  - genetic constructs known to integrate into the chromosome
  - gene editing
- For integrating products, the primary concern is malignant transformation.
- Delayed adverse events could include other immunological and nonimmunological toxicities.

## Long Term Follow-Up After Administration of Human Gene Therapy Products Guidance for Industry

January 2020

- Informed consent document must explain:
  - the purpose and duration of LTFU observations
  - the time intervals, and the locations of scheduled study visits contact
  - details as to what those contacts will involve
- “You must promptly investigate all safety information you receive (21 CFR 312.32(d)(1)).”
- “You must also revise your informed consent document and Investigator Brochure to include the new adverse event(s) that may be associated with the product or study procedures (21 CFR Part 50, 21 CFR 312.55(b)).”



# **Common Risks in Human Gene Transfer Research**

# Components of Gene Transfer Products



Most gene transfer products are comprised of two molecular features:

- 1) One or more transgenes- genetically engineered DNA or RNA sequence encoding therapeutic protein(s).
- 2) A delivery method, for example:
  - 1) *Ex vivo* manufactured cellular product (such as CAR-T)
  - 2) Viral vector (AAV, Adenovirus, lentivirus, etc.)
  - 3) Nanoparticles / LNP

**Many significant risks of gene therapy may pertain to the transgene and/or to the delivery method.**



# Examples of Specific Risks

Certain risks pertain to the **transgene**

- Encoded protein may induce dose limiting toxicities
  - e.g. overexpression of clotting factors → risk of thrombosis
- Encoded protein may alter the chromosome
  - Nucleases and integrases
- Encoded protein may be immunogenic (especially in gene replacement therapy).
  - May cause inflammatory reactions in target tissue.
  - May produce immune response that interferes with other current or future therapies
- Risk assessment
  - Molecular analysis of transgene
  - Preclinical data if relevant animal models exist
  - Prior experience with similar investigational products

# Examples of Specific Risks



Certain risks pertain to the **delivery method / vector**

- Immune effector cells cause on-tumor and off-tumor inflammatory effects
  - Cytokine Release Syndrome (CRS)
  - Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- *Ex vivo* modified cells may be malignant or prone to malignant transformation
- Nanoparticle components may be toxic or immunogenic
- Vector classes that modify the chromosome pose risk of insertional mutagenesis
  - Retroviruses and lentiviruses
  - Vectored gene editing nucleases
  - Retrotransposons

# Examples of Specific Risks



Certain risks pertain to the **delivery method / vector**

- Immune responses to a vector
  - Interfere with dose escalation studies
  - Interfere with estimation of minimal effective and maximum tolerated dose
  - May interfere with future eligibility for more effective therapies



# Severe Adverse Events in AAV Vector Clinical Trials

Toxicity	Serious Adverse Event	Vector Stereotype	Indication	Route of Administration
<b>Hepatotoxicity</b>	Elevated liver enzymes, serious liver injury	AAV9	SMA	Intravenous
	Elevated liver enzymes	AAV5	Hemophilia	Intravenous
	Liver failure	AAV8	XLMTM	Intravenous
<b>TMA</b> thrombotic microangiopathy	Thrombocytopenia, hemolytic anemia, acute kidney injury	AAV9	SMA, DMD	Intravenous
<b>Neurotoxicity</b> (DRG Histopathology)	DRG neuronal loss	AAV9	GAN	Intrathecal
<b>Neurotoxicity</b> (DRG Histopathology)	DRG neuronal loss	AAVrh10	ALS due to mutation in SOD1	Intrathecal
<b>Neurotoxicity</b> (Brain MRI)	Abnormal T2 hyperintensities	AAVrh10	Late infantile Batten disease	Intraparenchymal

[www.fda.gov](http://www.fda.gov)

Tfv1A, thrombotic microangiopathy; DRG, dorsal root ganglion; SMA, spinal muscular atrophy; XLMTM, X-linked myotubular myopathy; DMD, Duchenne muscular dystrophy; GAN, giant axonal neuropathy; ALS, amyotrophic lateral sclerosis; *SOD1*, superoxide dismutase 1 gene



# **Gene Editing and Related Technologies**

# August 2023 Proposed Changes to *NIH Guidelines*



## Proposed changes recently announced in the Federal Register

- Most proposed changes are not related to clinical trials.
- Proposed changes do not directly involve Informed Consent.

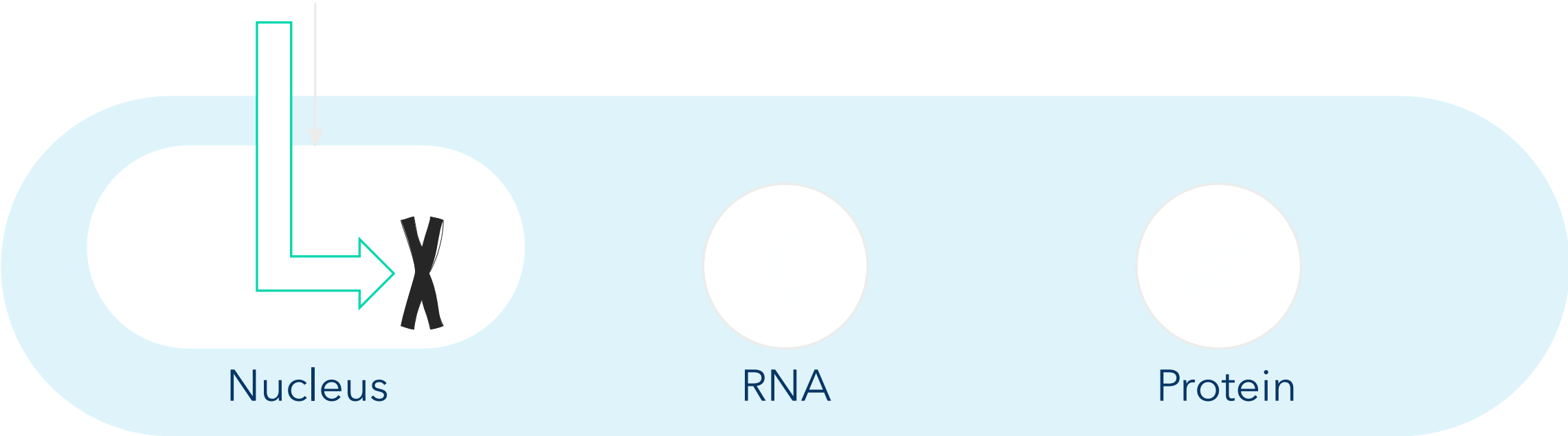
Proposed changes to *NIH Guidelines* Section III-C do expand the definition of Human Gene Transfer research.

Expanded definition would encompass certain **gene editing** and related techniques not currently included in the definition of HGT.

# Gene editing re-writes genetic code



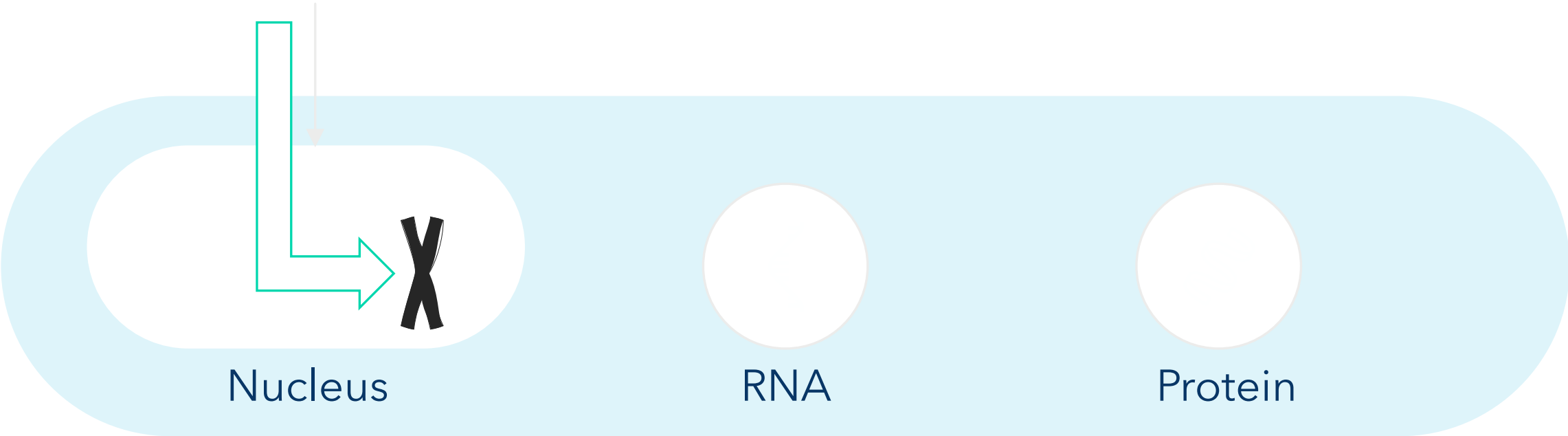
CRISPR and similar technologies have the potential to precisely add and delete genetic information from the chromosome.



# Gene editing re-writes genetic code



Certain gene editing approaches not currently subject to *NIH Guidelines* will qualify as HGT if proposed changes are implemented.





# Gene editing re-writes genetic code



Therapeutic **somatic cell editing** is part of current trials in clinic.

Intentionally heritable human **germ-line editing** is not allowed in clinical trials and not addressed here.



# Potential Risks of Gene Editing and Related Technology



Approaches to modify DNA include Gene/ Genome editing, Base editors, and Prime editors.

- Errors may result in off-target edits, deletions and translocations of chromosomal DNA.
- Current methods for detecting errors have incompletely defined sensitivity.
- Clinically acceptable error rate is undetermined.

Gene editing may be applied *ex vivo* or *in vivo*.

- *Ex vivo*
  - actual editing errors easier to determine.
  - risk of preferential expansion due to rare oncogenic events may be greater.
- *In vivo*
  - Tracking on / off target delivery to specific tissue is difficult.
  - Risk of accidental effects on germ line cells is potentially greater.

# Potential Risks of Gene Editing and Related Technology



“ Prior to enrolling, subjects should be asked to provide voluntary, informed consent to long term follow-up. ”

*-Human Gene Therapy Products Incorporating Human Genome Editing. Draft Guidance for Industry. March 2022*



# Participant Perspectives

# Informed Consent - Patient Advocate Viewpoints



## Frequently expressed concerns from patients and advocates

- IC forms are too long.
- Science of gene transfer difficult to understand.
- Difficult for nonexperts to assess:
  - Risk and benefit of complex interventions.
  - Objectivity of information from sponsor or investigators.

## Improving patient informed consent for haemophilia gene therapy: the case for change

Laurence Woollard, Richard Gorman, and Dakota J. Rosenfelt  
Ther Adv Rare Dis 2021, Vol. 2: 1-16

### Concerns:

- Information overload
- Therapeutic misconceptions
- Therapeutic optimism and hype
- "Patients' desire for improvement in health-related QoL in feasibly desperate medical circumstances can undermine their decisional capacity."

### Solutions:

- Visual aids
- FAQ lists of patient questions and concerns
- Standardized lexicon of preferred terminology

# Enhancing Signal-to-Noise in Informed Consent Process

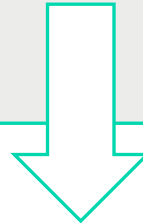
Detailed Speculative Risk Assessments

Technical Molecular Information

Comprehensive biomedical analysis

**ICD Composition & Review**  
Authors, Regulators, IRB, IBC

Due Diligence



## Informed Consent Process

- ✓ **Plain language**
- ✓ **Focus on information likely to affect willingness to participate**
- ✓ **Technical resources available for those who ask**



# **Unsolved Problems in Informed Consent**



# Shedding, Community Exposure, and Third-Party Risk



- For some gene transfer products, genetically modified agents are expected to be “shed” from injection site or in body fluids
- Per FDA Guidance\* monitoring for shedding is often warranted although risk of transmission is usually “extremely low probability.”
- Exposure to intimate contacts or general public may imply hypothetical potential harm.
  - Theoretical risks may include seroconversion of siblings affected with inherited condition, rendering the sibling ineligible for treatment.
- Sponsors and investigators may provide hygiene / shedding control instructions for participants.
  - Who should review these?
  - It is likely that IRBs and IBCs have complementary viewpoints and expertise.

*\*Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products, Guidance for Industry, August 2015 & Recommendations for Microbial Vectors used for Gene Therapy, Guidance for Industry, September 2016*

# Shedding, Community Exposure, and Third-Party Risk



## SACHRP Recommendations

- HHS Secretary's Advisory Committee on Human Research Protections advises that IRBs may consider risk to nonsubjects, while avoiding unnecessary or duplicative review.\*
- Consideration for:
  1. probability
  2. foreseeability
  3. magnitude.

\*The Protection of Non-Subjects from Research Harm, SACHRP Secretary's Advisory Committee on Human Research Protections, March 2022.

Young children or neonates may be enrolled in clinical trials with planned 15-year follow up.

- At what ages are assent and re-assent recommended?
- How should child participants be informed of new information over the course of LTFU?
- How are complex scientific issues communicated in an age-appropriate manner?
- How is right to withdraw communicated in an age-appropriate manner?

- *Cell and Gene Therapy* can encompass a very wide range of investigational products, each with specific risks and concerns for human subject protection.
- Various types of gene therapies involve class risks common to the vector or modality.
- Each gene therapy involves specific transgenes that require careful evaluation based on known biology.
- Preparing an ICD to address complex biology is challenging and likely to require several iterations.
- Useful guidance has been published by FDA, NIH, professional organizations and patient advocacy groups.
- IRBs and IBCs can work together to optimize ICD reviews.

# Thank you!



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