The ethical conduct of cell and gene therapy research: Novel challenges and ethical considerations for researchers and regulators (REC, UNCST & NDA)

Joint Clinical Research Centre

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Cissy Kityo Mutuluuza,
MBChB, MSc, PhD, FUNAS, DSc
Executive Director, JCRC

Gene Therapy Flavors and Indications

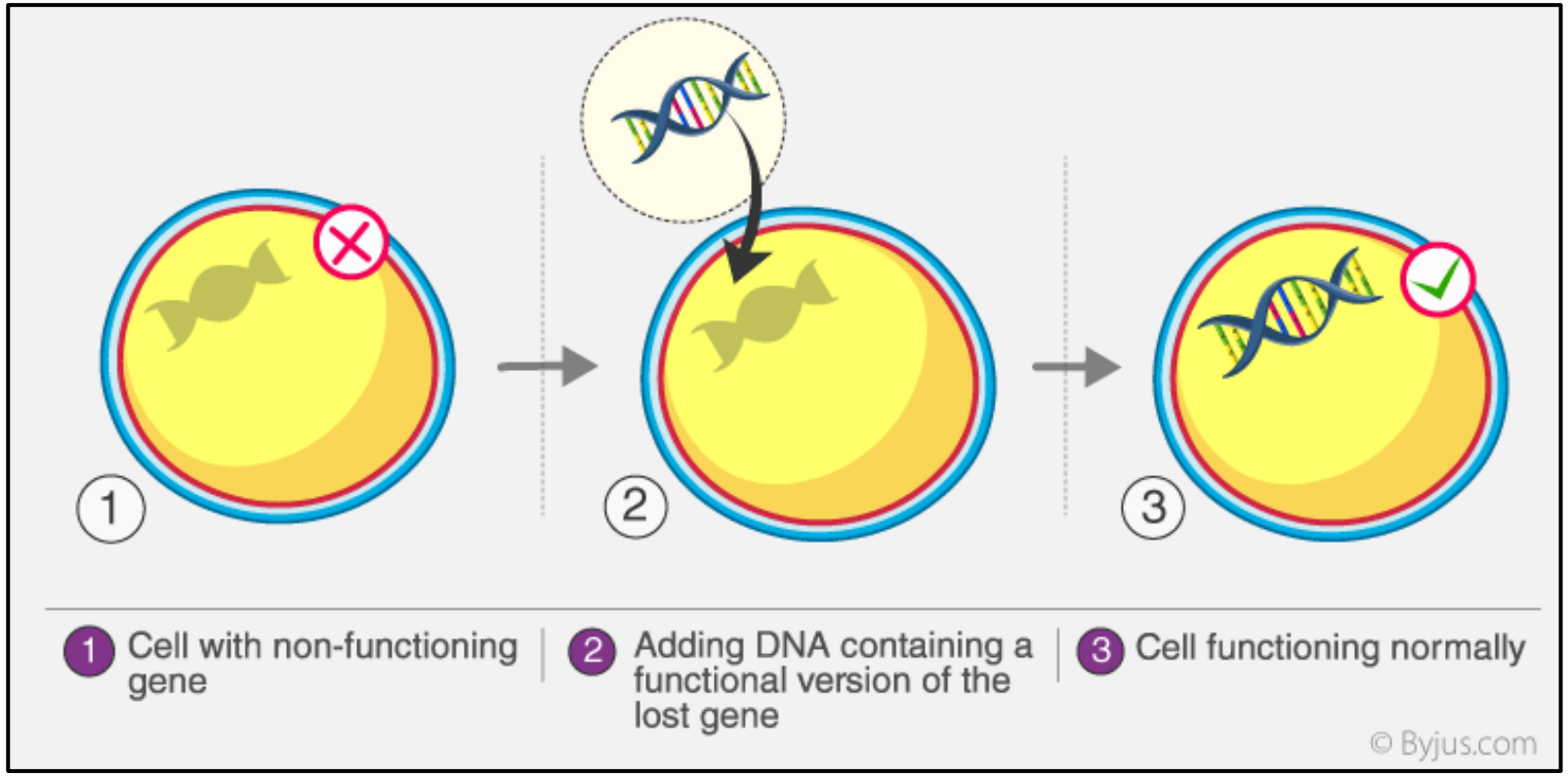
What is gene therapy?

Gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.[1]

Alterations can include:

- Inactivation or deletion of disease-causing gene
- Replacement with a healthy copy of gene
- Insertion of a new or modified gene

Somatic editing modifies non-reproductive cells.



[1]FDA definition

The potential of gene therapy

1. Genetic therapies focus on underlying disease biology, rather than symptom management. If the genetics are known, there is no need to identify small molecules that can treat, gene therapy can immediately be developed for treatment or cure.

2. Genetic therapies could be a one-time treatment with transformational and curative potential.

3. First **32** gene therapies approved by the U.S. FDA and EMA. FDA anticipates 10-20 new approvals per year by 2025.

4. As of 2022, there were 1,221 active clinical trials of gene therapies which are designed to treat >100 different diseases worldwide. (Statista.com; *Number of active trials for cell and gene therapies worldwide 2022 by trial phase,* Published by Matej Mikulic, Nov 23, 2022)

Indications for gene therapy

Any disease with a biological understanding for which manipulation of genetic material could provide cure, treat an unmet need or transform disease course and health outcome.

- Inherited diseases, especially if monogenic (single-gene defect)
- Malignant diseases, regardless of genetic basis
- Infectious diseases

At present, **germline editing** (editing reproductive cells or early embryos), is considered too risky and a moratorium has been called for and agreed upon by multiple countries. (Nature_Moratorium_2019)

Current federal law in the U.S. and WHO prohibit any applications "in which a human embryo is intentionally created or modified to include a heritable genetic modification."

Gene Therapy: A New Era in Medicine

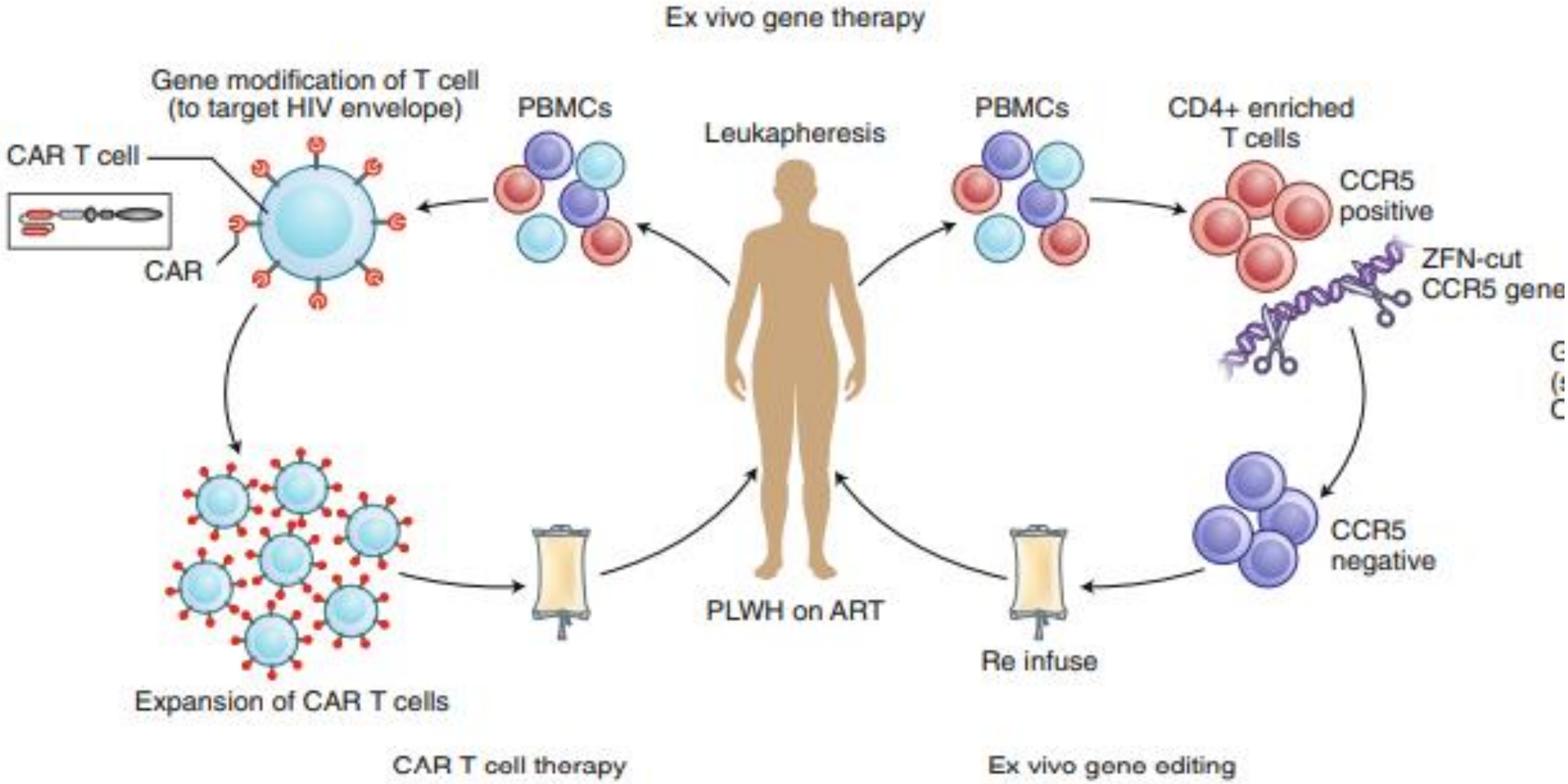
- Gene therapy represents a paradigm shift in medicine moving from treating symptoms to curing diseases at their genetic root
- Curative Potential for Previously Incurable Diseases (HIV, Sickle Cell Disease, Cancers)
- There are over 30 approved gene therapy products on the market

- **Relevance to Africa's Health Burden**
- Africa has a high prevalence of genetic and infectious diseases, and a young population making gene therapy especially impactful:
  - Over 300,000 babies born annually with SCD in Sub-Saharan Africa
  - Millions living with HIV/AIDS
  - Rising rates of cancer and non-communicable diseases
- Gene therapy offers hope for durable, cost-effective solutions that reduce long-term healthcare costs and improve quality of life.

In vivo versus ex vivo gene therapy

- Ex vivo gene therapy takes cells from the body, administers the gene therapy to the cells in a laboratory, and then returns those cells to the body.
- In vivo gene therapy delivers genetic material directly to living cells inside the body.

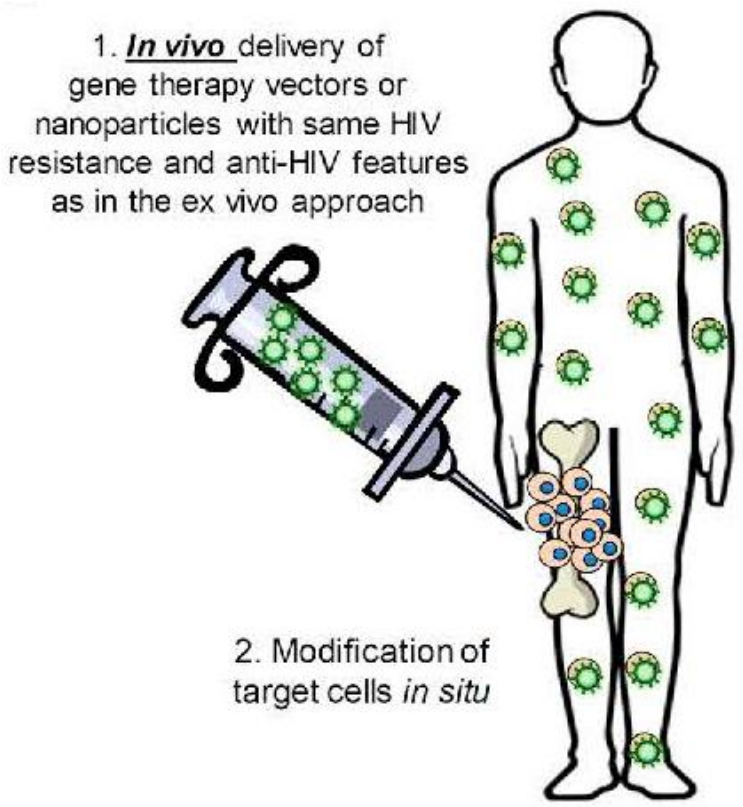
Intermediary Stage; Ex-vivo gene therapy



Ideal target product profile for an HIV cure

- "Single-shot" (administered simply and percutaneously in an outpatient setting)

In vivo delivery of curative interventions



Peterson and Kiem, *Cell Stem Cell* 2019

First 7 gene therapies approved globally include both in vivo and ex vivo approaches for cancer and inherited diseases

Tradename (proper name)	Date of Approval	Approving Agency	Indication	Manufacturer	Delivery Route	Vector
Gendicine	October 2003	State Food and Drug Administration of China	Head and neck squamous cell carcinoma	Shenzhen SiBione GeneTech (Shenzhen, China)	In vivo; intratumoral or intracavital injection or intravascular infusion	Adenovirus (Ad) encoding a tumor suppressor gene (p53)
Glybera® (alipogene tiparvovec)	November 2012	European Market Authorization (EMA)	Lipoprotein lipase deficiency	uniQure (Amsterdam, Netherlands)	Intramuscular injection	Adeno-associated virus (AAV) serotype 1 encoding functional LPL gene
Strimvelis™	June 2016	EMA	Adenosine deaminase deficiency (ADA-SCID)	GlaxoSmithKline (Middlesex, U.K.)	Ex vivo; autologous transduced CD34+ hematopoietic cells	Retroviral vector encoding the adenosine deaminase gene (ADA)
Kymriah™ (tisagenlecleucel)	August 2017	U.S. Food and Drug Administration (FDA)	Acute lymphoblastic leukemia	Novartis Pharmaceuticals (Basel, Switzerland)	Ex vivo; autologous transduced T cells	Lentiviral vector encoding a chimeric antigen receptor (CD19 CAR)
Yescarta™ (axicabtagene ciloleucel)	October 2017	FDA	B-cell lymphoma	Kite Pharma Inc. a Gilead Company (Santa Monica, California, U.S.)	Ex vivo; autologous transduced T cells	Lentiviral vector encoding a chimeric antigen receptor (CD19 CAR)
Luxturna (voretigene neparvovec-rzyl)	December 2017	FDA	Biallelic RPE65 mutation-associated retinal dystrophy	Spark Therapeutics, Inc. (Philadelphia, PA, U.S.)	In vivo; subretinal injection	AAV encoding functional RPE65 gene
Zolgensma® (onasemnogene abeparvovec-xioi)	May 2019	FDA	Infantile onset spinal muscular atrophy (SMA) caused by biallelic SMN1 mutation	AveXis Inc. (Bannockburn, IL, U.S.)	In vivo; intravenous injection	AAV gene encoding functional SMN1 gene

Appropriate vectors to administer gene therapy

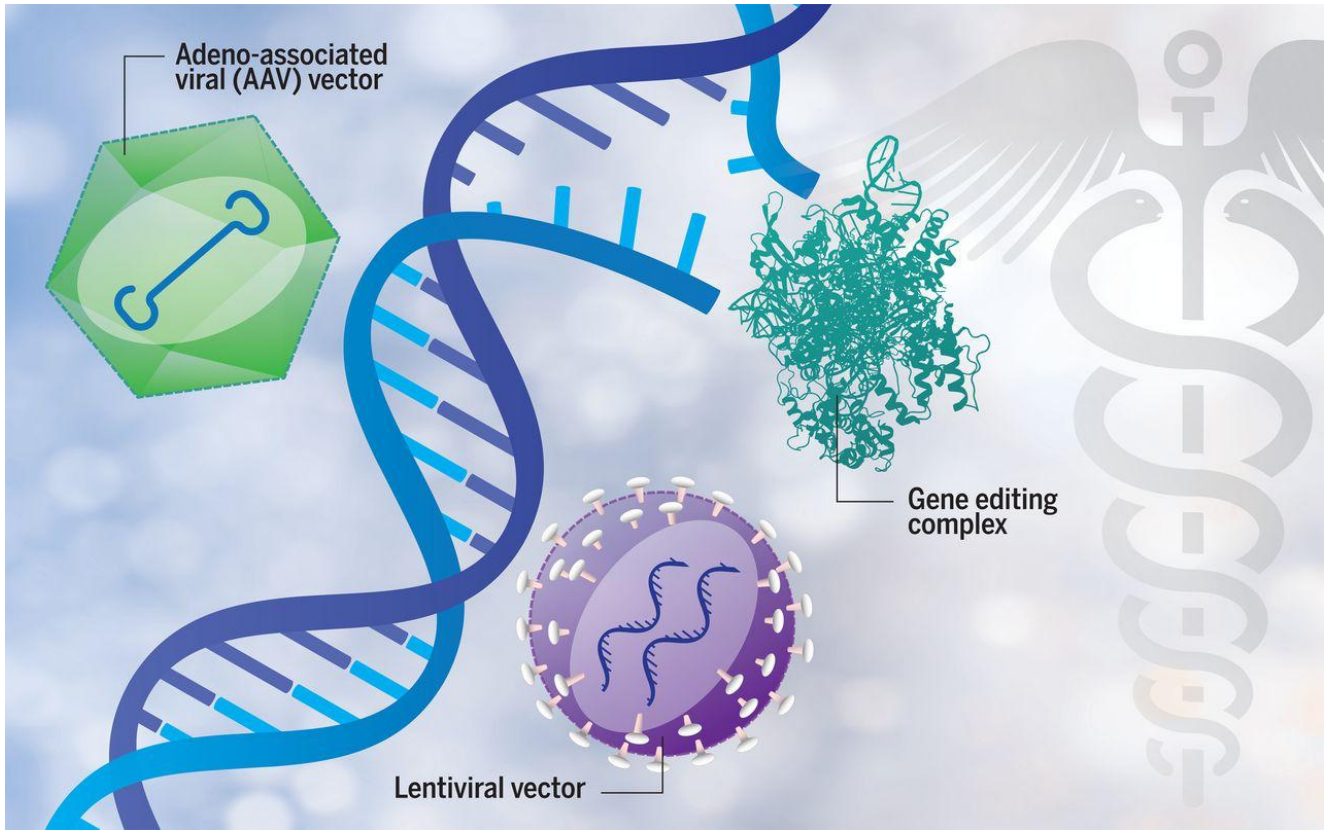
Today, most gene therapies are administered by adeno-associated viruses (AAV) vectors or lentiviral vectors (LV)

Three essential tools for human gene therapy.

- AAV and LV are the basis of several recently approved gene therapies.
- Gene editing technologies are in their translational and clinical infancy but are expected to play an increasing role in the field. (First FDA review of CRISPR in progress with decision expected in 2024).

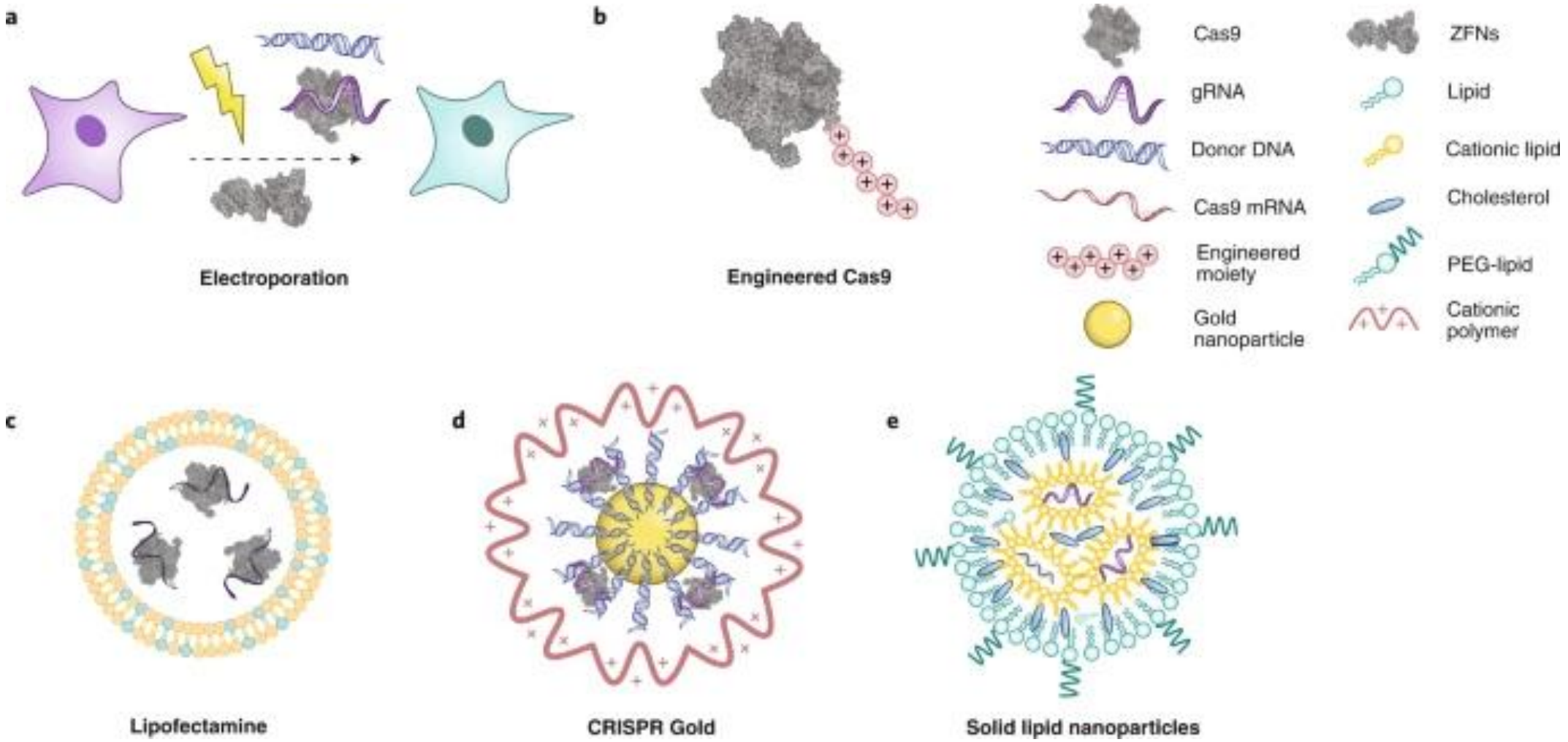
The type of vector to use depends on several factors:

1. Will the cell receiving the gene therapy divide over the patient's lifetime?
   a. If yes, need integrating LV or gene editing of cellular DNA
   b. If no, then gene therapy can be administered with non-integrating vector such as AV or AAV.
2. How big is the gene therapy payload to be delivered?
3. What cells need the gene therapy?



*Science*_Gene therapy comes of age_2018

Overview of nonviral methods to deliver gene editing cargo

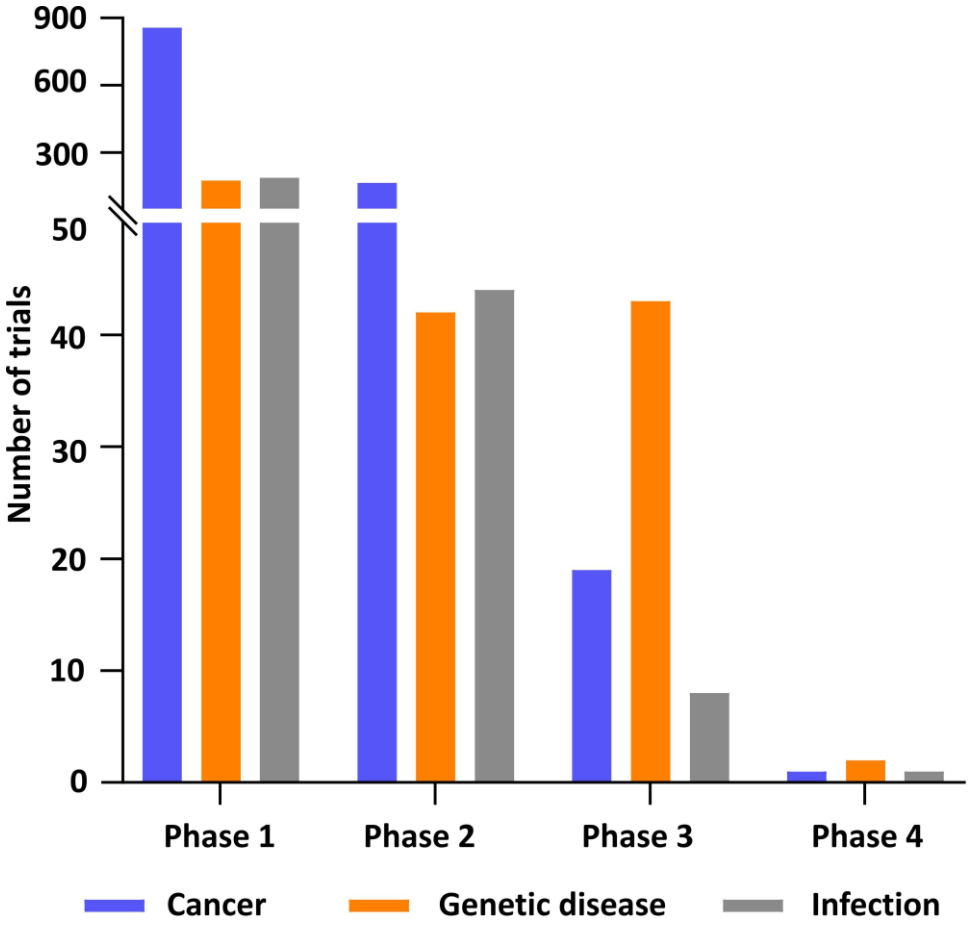


a, Electroporation is a highly effective means to deliver mRNA or nuclease protein in vitro. **b**, In addition, nuclease proteins can be recombinantly or covalently modified to enhance delivery properties, such as cell binding or nuclear entry. **c**, **d**, Lipofectamine (**c**) and gold nanoparticles (**d**) have been used to deliver nuclease mRNA, protein and gRNAs. **e**, Because of previous advances in siRNA delivery, SLNs are currently the most advanced non-viral vehicles for genome editing cargo delivery in vivo.

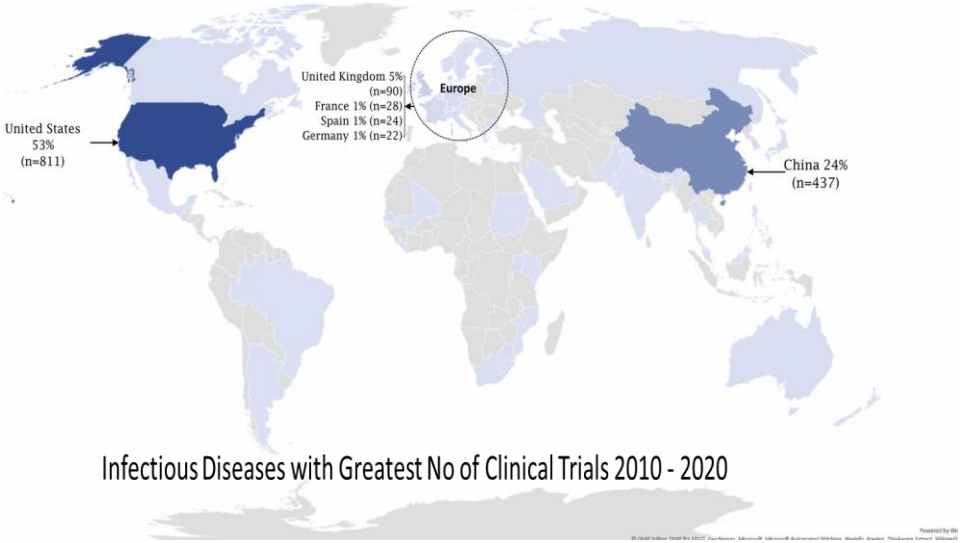
*Nature Biotechnology*_The Delivery Challenge_2020

Gene Therapy Research and Development in LMICs

LMIC are Currently Excluded from Gene Therapy Development



Arabi et al., 2022: *Gene therapy clinical trials, where do we go? An overview*



Target	No of Clinical Trials
HIV	62
COVID-19	29
Malaria	20
Ebola	19
Hepatitis C	13
Human Papillomavirus	12
Hepatitis B	10

Since 1994, 3,900+ Gene Therapy Clinical Trials across 46 countries have been registered

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THE NUMBER OF GENE & CELL THERAPY TRIALS WHICH HAVE TAKEN PLACE IN AFRICA:

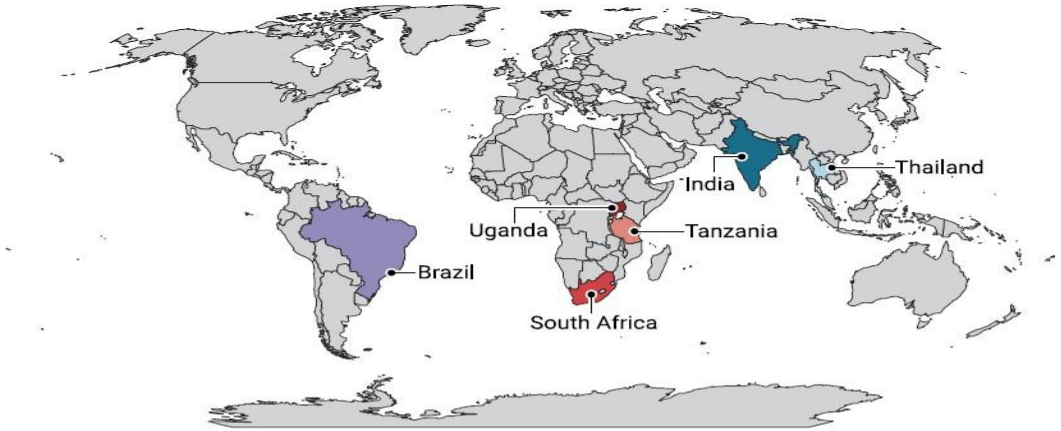
0

Adoption of Cell and Gene Therapy in Africa is inevitable and will grow with ethical concerns about safety, efficacy, and accessibility

GENE THERAPY

The translational gap for gene therapies in low- and middle-income countries

Kevin W. Doxzen[1]*, Jennifer E. Adair[2,3], Yris Maria Fonseca Bazzo[4], Daima Bukini[5,6], Kenneth Cornetta[7], Varsha Dalal[8], Renato Luiz Guerino-Cunha[9,10], Suradej Hongeng[11], Geeta Jotwani[12], Cissy Kityo-Mutuluuza[13], Krishnamurti Lakshmanan[14], Johnny Mahlangu[15], Julie Makani[5,6,16], Vikram Mathews[17], Margareth C. Ozelo[18], Savita Rangarajan[19,20], Janine Scholefield[21,22], João Batista Silva Júnior[23,24], Joseph M. McCune[25]



Brazil
Population 215.3 million

Hemophilia: 13,618 people living with hemophilia

Number of new cases per year:
Leukemia: 11,859
Non-Hodgkin's lymphoma: 11,093
Multiple myeloma: 5757
Hodgkin lymphoma: 2667

India
Population 1.4 billion

Number of new cases per year:
Leukemia: 49,883
Non-Hodgkin's lymphoma: 39,736
Multiple myeloma: 16,526
Hodgkin lymphoma: 9611

Thailand
Population 71.7 million

β-Thalassemia: 6480 infants born each year with severe β-thalassemia

Uganda
Population 47.3 million

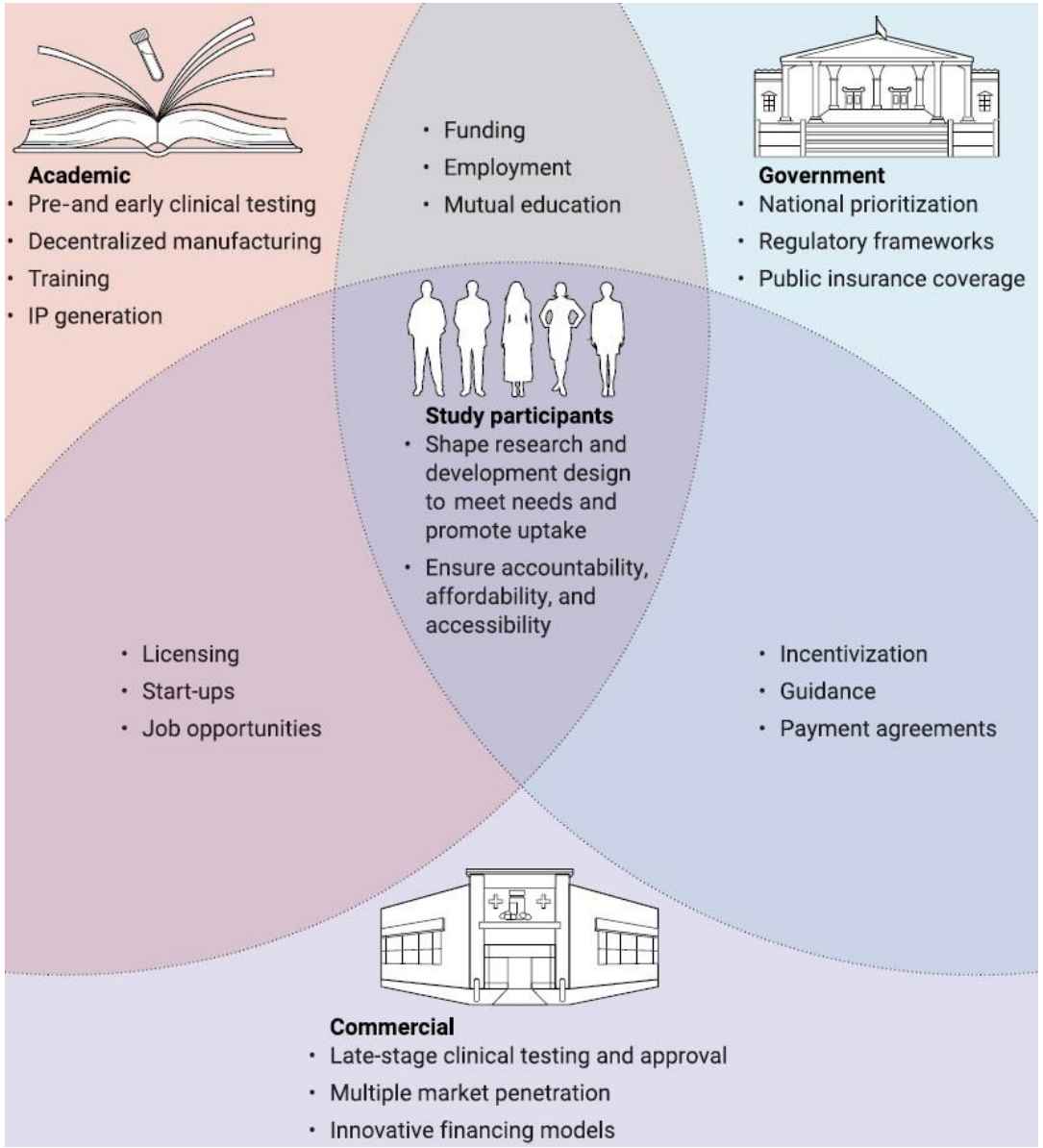
HIV: 1.4 million adults ≥15 years old living with HIV

South Africa
Population 59.9 million

Hemophilia: 2404 people living with hemophilia

Tanzania
Population 65.5 million

SCD: 11,000 infants born each year with SCD



Doxzen KW, Adair JE, Fonseca Bazzo YM, Bukini D, Cornetta K, *et al*. The Translational Gap for Gene Therapy in Low and Middle-Income Countries. *Sci Transl Med* 2024; 16 (746): eadn 1602.

Gene Therapy Policy and Regulations

FDA

Regulation & Policy

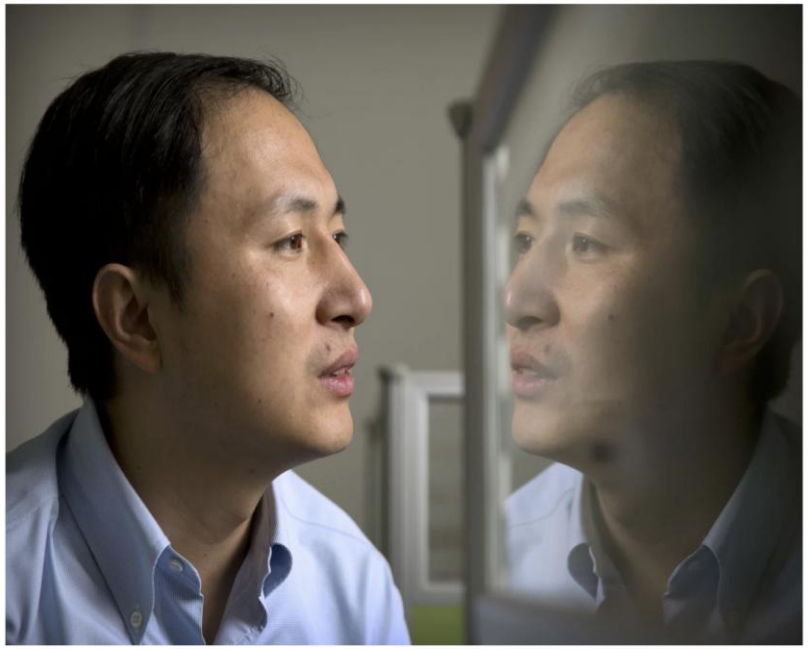
Infrastructure for Commercialization

GGTI
GLOBAL GENE THERAPY INITIATIVE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

World Health Organization

Background



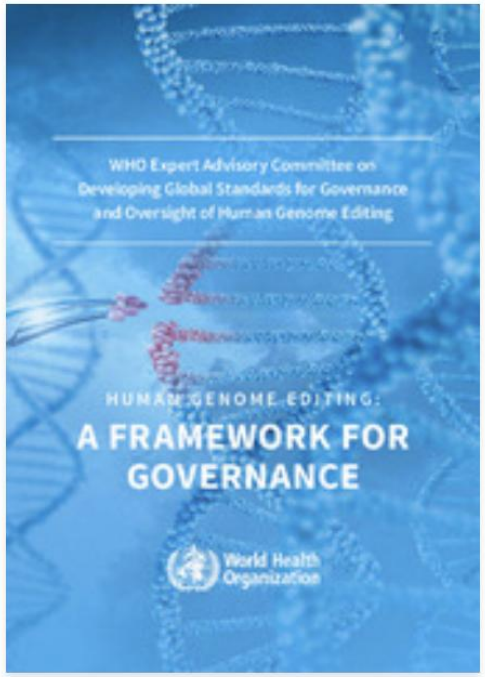
Genetics researcher He Jiankui said his lab considered ethical issues before deciding to proceed with DNA editing of human embryos to create twin girls with a modification to reduce their risk of HIV infection. Critics say the experiment was premature.

Mark Schiefelbein/AP

- **Nov 2018:** A Chinese scientist claimed to make the world's first genome-edited babies (twin girls)
- Their genome was edited to disable the pathway HIV uses to infect cells
- Controversial reactions to this development due to safety and ethical concerns of using the technology outside the research context especially embryonic research
- **Dec 2018:** WHO established a global multi-disciplinary expert panel to examine the scientific, ethical, social and legal challenges associated with human genome editing (both somatic and germ cell).

The Expert Advisory Committee on Developing Global Standard for Governance and Oversight of Human Genome Editing:

Developed Three Documents:



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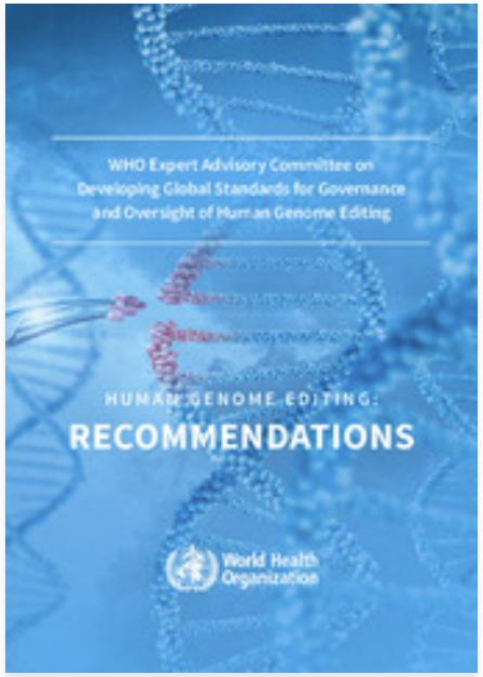
https://www.who.int/publications/i/item/9789240030060



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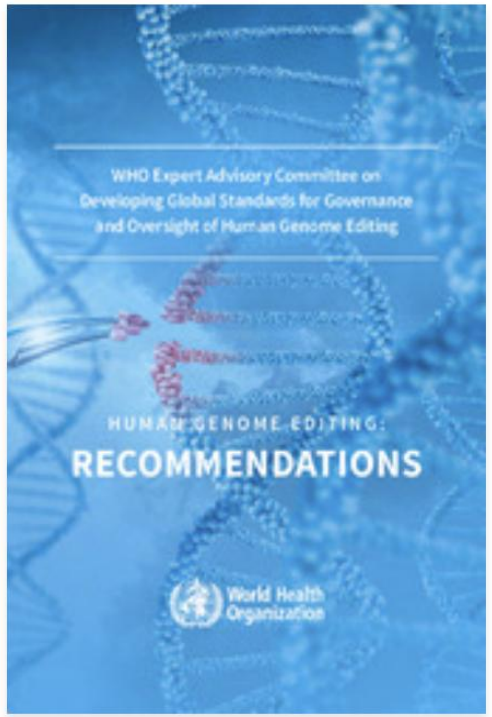
https://www.who.int/publications/i/item/9789240030404

Recommendations:



The Committee produced a series of recommendations in nine discrete areas:

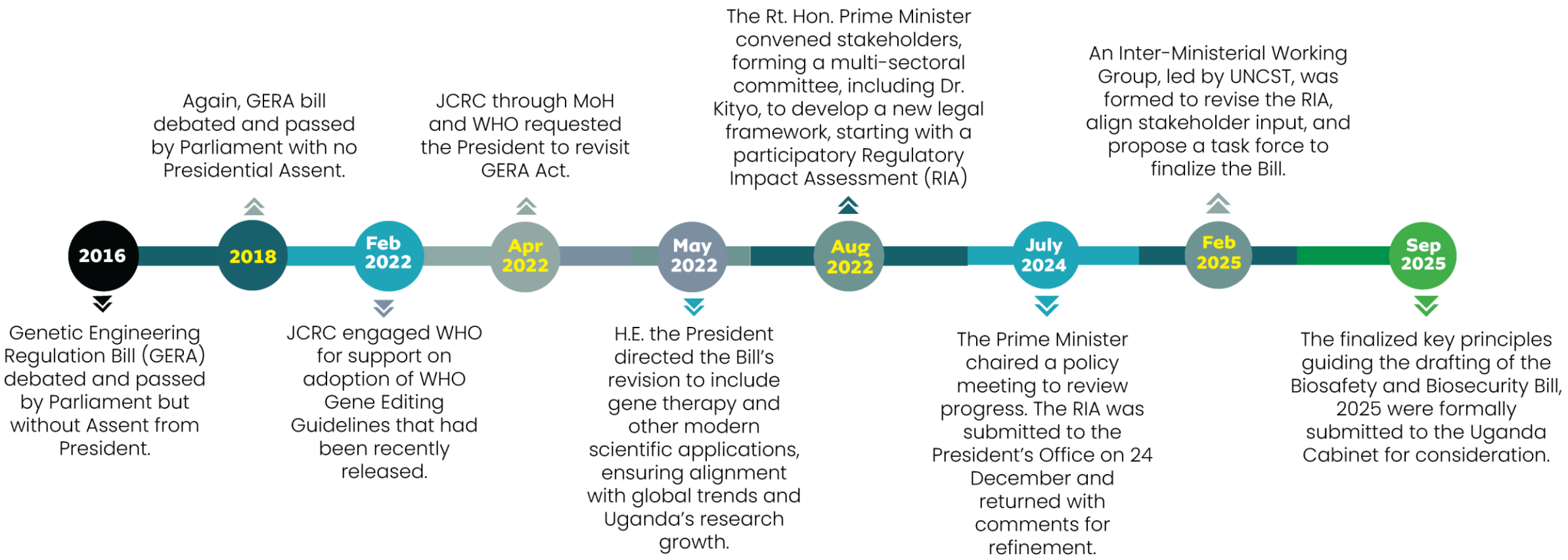
1. Leadership by the WHO and its Director-General
2. International collaboration for effective governance and oversight
3. Human genome editing registries
4. International research and medical travel
5. Illegal, unregistered, unethical or unsafe research and other activities
6. Intellectual property
7. Education, engagement and empowerment
8. **Ethical values and principles for use by WHO**
9. Review of the recommendations

Position Paper:

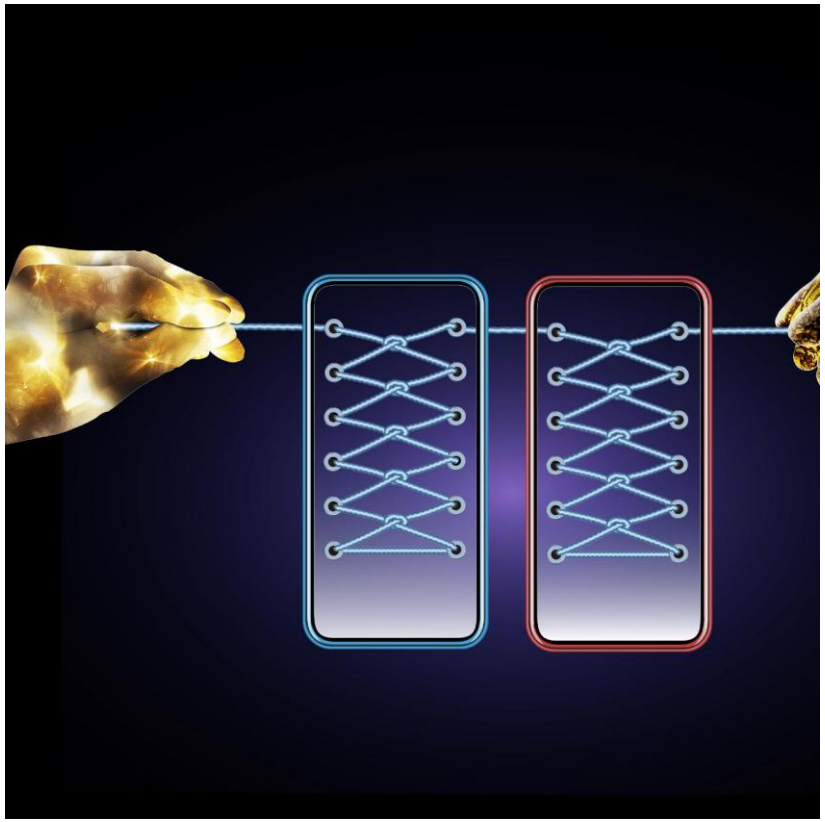
Preventing premature use of human genome editing:

To help ensure heritable human genome editing does not proceed prematurely to clinical trials, the Committee recommended, and the WHO Director-General subsequently made, a policy statement in July 2019 clarifying that "it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing."

Advancing Gene Therapy Legislation in Uganda



Novel Ethical Dilemmas in Cell and Gene Therapy



Informed Consent Challenges

Genetic modification trials complicate informed consent due to participants' limited understanding of long-term effects.

Risk-Benefit Analysis Complexity

First-in-human studies carry uncertain benefits and unknown risks, complicating ethical risk-benefit evaluations.

Equity and Access Issues

Access to advanced therapies is limited in low- and middle-income countries, raising equity concerns.

Privacy and Data Protection

Protecting genetic data privacy is critical to prevent misuse and discrimination in cell and gene therapy.

Ethics Discussion Questions

Key principles include autonomy, beneficence, non-maleficence, and justice to protect research participants

Cell and gene therapy require rigorous ethical oversight due to unique risks and complexities.

INFORMED CONSENT

How do we know if/when we have achieved informed consent, especially when long-term consequences may be unknown?

MEDICAL NECESSITY

What criteria stand out to determine when a cell and gene therapies can be ethically justifiable?

ENSURING SAFETY AND MINIMIZING UNINTENDED CONSEQUENCES

How can we ensure the safety of cell and gene therapies?

SOCIAL IMPLICATIONS

What are some of the broader social implications of cell and gene therapies?

Could cell and gene therapies deepen inequalities?

GOVERNANCE

What role should regulatory bodies play in cell and gene therapy research?

Should different countries have different regulations?

Who is responsible for oversight?

Ethical Considerations for Cell and Gene Therapy

Favorable Risks and Benefits Balance

The choice of whether to use gene therapy is about risk-to-benefit ratio for a given disease circumstance

Risk/benefit assessment is one of the fundamental requirements in ethical review of research involving human participants (Aarons)

Research must have higher chance of doing good, overall, than doing harm*

Researchers should minimize risks and maximize benefits

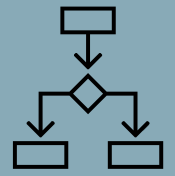
Need to protect participants from excessive risks

Difficult to evaluate because there can be asymmetries

Ethical Considerations for Cell and Gene Therapy

Other Things to Consider in Evaluating Risks

Innovativeness of interventions



Modes of actions

Nature of the target

Relevance of animal models (pre-clinical evidence)

Stronger evidentiary justification needed for specific groups

Uncertainty (major hallmark of FIH studies)

Risk-Benefit Assessment and Justification

RISKS

Indeterminate risks

Controversial risk-benefit justification based on limited safety and efficacy data

Some risks manageable whereas some harms may be irreversible

- Physical risk
- Psychological, moral, financial, social and legal risks
- Risks of omission (e.g., use of placebo controls in trial designs)
- Probability, duration and magnitude of their effects

Risks of "me too" drugs more predictable than those of innovative interventions

BENEFITS

Direct Benefits (expected medical benefits)

- ☐ Expected to be minimal
- ☐ Parameters are questionable (e.g., tumor shrinkage, life expectancy)
- ☐ Use of psychological benefits is debatable

Indirect or collateral benefits

Aspirational benefits (to society or future patients)

- ☐ Refers to access to medical care

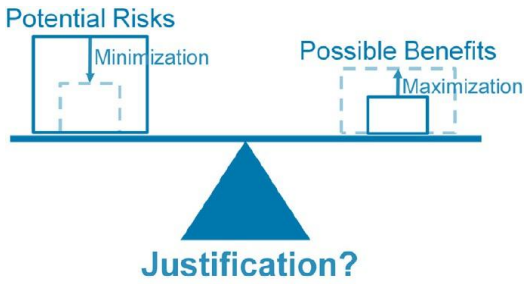
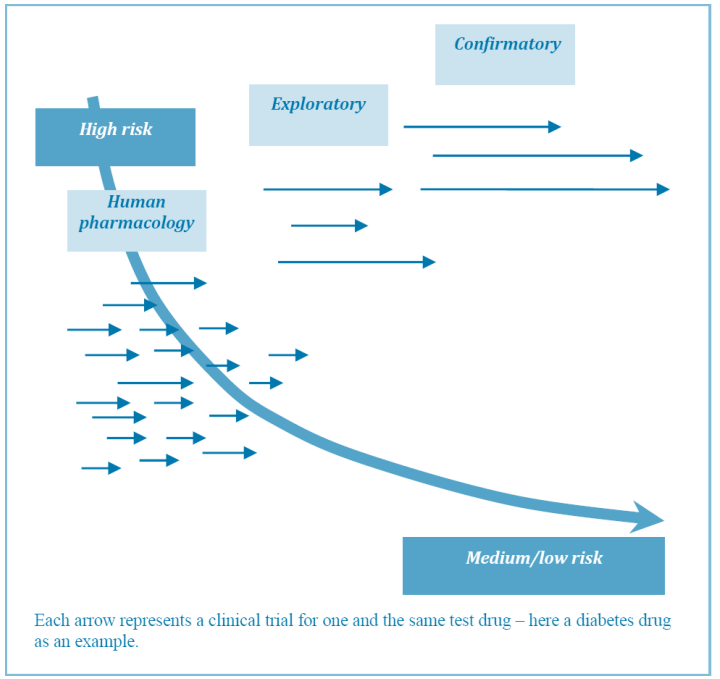


Fig 1. Risk-benefit assessment and justification.



Each arrow represents a clinical trial for one and the same test drug – here a diabetes drug as an example.

Karlberg JPE, Speers MA. Reviewing Clinical Trials: A Guide for The Ethics Committee. 2010. 153 pages. Available at: https://books.google.com/books/about/Reviewing_Clinical_Trials.html?id=wGz2cQAACAAJ

Koonrungsesomboon N, Laothavorn J. Karbwang J. Ethical Considerations and Challenges in First-in-Human Research. *Translational Research* 2016; 177: 6 – 18.

HIV Gene Therapy Strategies and Safety: What do we know from the Recent Publications?

Silvere D. Zaongo[1,2], Huan Xia[1,3] and Ping Ma[1,3,4]*

[1]Department of Infectious Diseases, Tianjin Second People's Hospital; [2]International School of Medicine, Tianjin Medical University; [3]Tianjin Association of STD/AIDS Prevention and Control; [4]School of Medicine, Nankai University. Tianjin, China

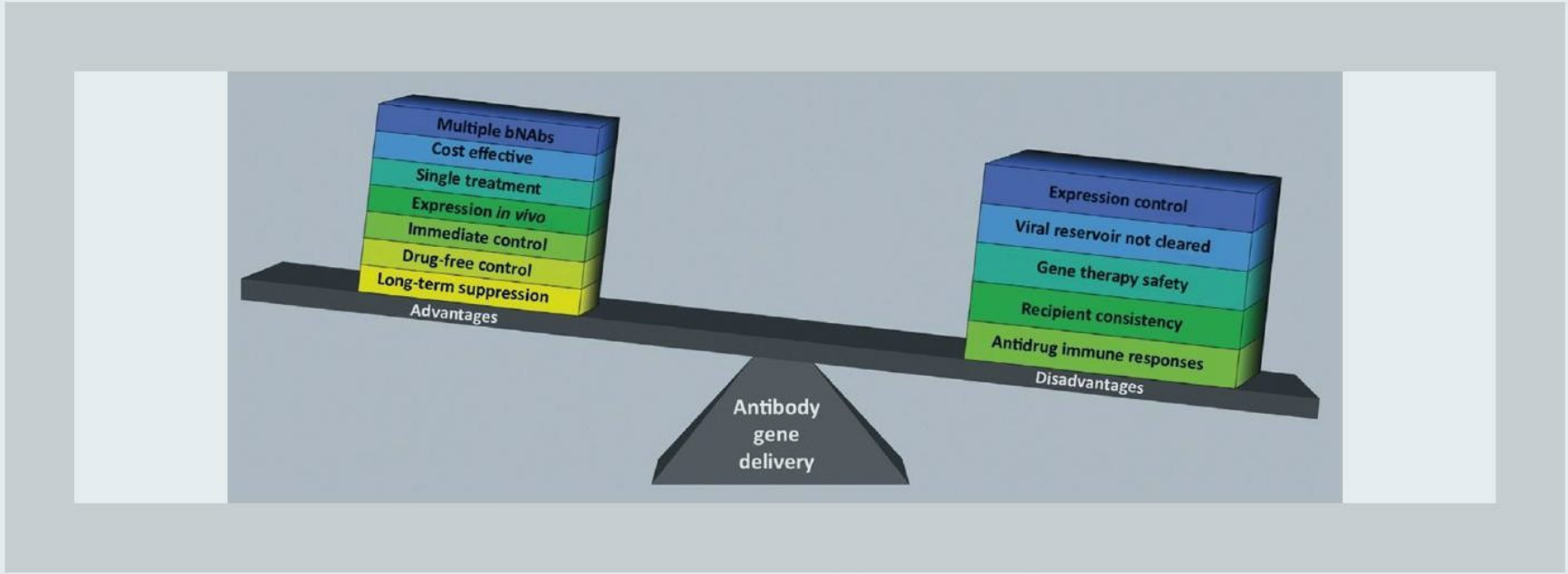


Figure 3. *Illustration of advantages and disadvantages of AVPs approach through antibody gene delivery method. HIV-1 broadly neutralizing antibody (bNAb) gene delivery has a number of potential advantages in preventing and treating infection, but these are countered by disadvantages that currently limit development. A functional cure based on this strategy may be possible if a balance can be reached to make the approach safe, feasible, and consistent among human recipients. From Haigwood and Hessell, 2019.[75]*

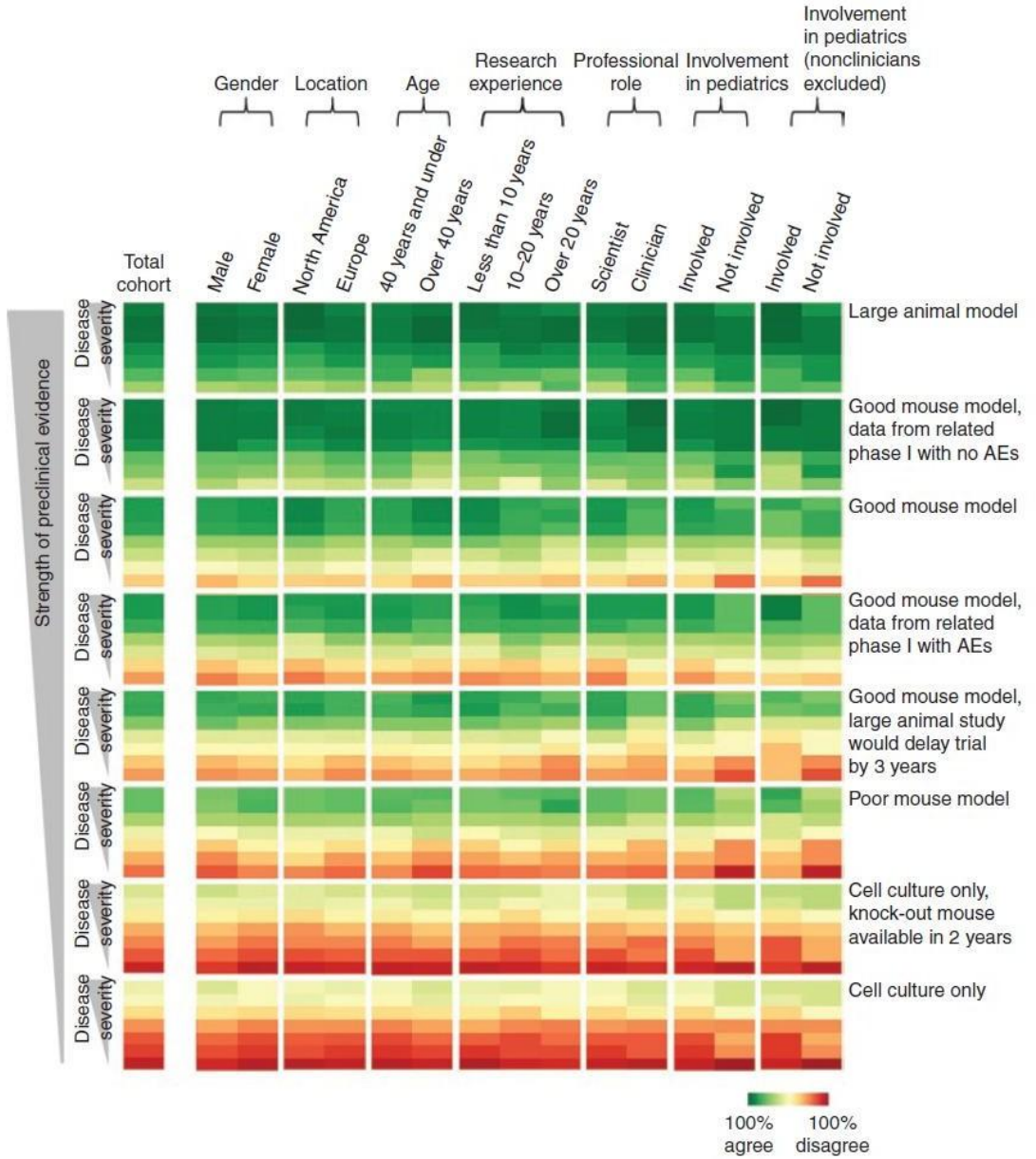
Zaongo SD, Xia H, Ma P. HIV Gene Therapy Strategies and Safety: What Do We Know from the Recent Publications? *AIDS Rev* 2020; 23(3): 165 – 202.

Gene Therapy Researchers' Assessments Of Risks And Perceptions Of Risk Acceptability In Clinical Trials

Claire T. Deakin[1,2], Ian E. Alexander[1,3], Cliff A. Hooker[2,4] and Ian H. Kerridge[2,5]

Table 4 Descriptions of preclinical evidence provided to respondents for decision-making about the initiation of a clinical trial

Abbreviated description of preclinical evidence	Description of preclinical evidence as provided to respondents in the survey instrument
Cell culture only	A statistically powered study demonstrating therapeutic efficacy in relevant primary human cells in culture AND evidence of safety in a validated cell culture assay
Cell culture only, knock-out mouse available in 2 years	A statistically powered study demonstrating therapeutic efficacy in relevant primary human cells in culture AND evidence of safety in a validated cell culture assay, if a knock-out mouse model is expected to be generated within 2 years
Good mouse model	A statistically powered study demonstrating safety and therapeutic efficacy, in correcting a mouse phenotype with no evidence of toxicity or adverse events in long-term follow up, using a mouse model where the phenotype is the same as the human disease (no large animal model available)
Poor mouse model	A statistically powered study demonstrating safety and therapeutic efficacy, in correcting a mouse phenotype with no evidence of toxicity or adverse events in long-term follow up, using a mouse model that involves the same gene but where the phenotype differs from the human disease (no large animal model available)
Good mouse model, large animal study would delay trial by 3 years	A statistically powered study demonstrating safety and therapeutic efficacy, in correcting a mouse phenotype with no adverse events, using a mouse model where the phenotype is the same as the human disease and when a large animal model is available but a large animal study would delay trial initiation by 3 years
Large animal model	A statistically powered study demonstrating safety and therapeutic efficacy in a large animal model, in correcting a disease phenotype that is the same as the human disease and with no adverse events in long-term follow up
Good mouse model and data from related phase I trial with no adverse events	Convincing preclinical safety and efficacy data in a mouse model and data from a phase I trial targeting a different disease of the same target tissue, which used the same technological intervention and demonstrated therapeutic efficacy and no adverse events
Good mouse model and data from related phase I trial with low frequency adverse events	Convincing preclinical safety and efficacy data in a mouse model and data from a phase I trial targeting a different disease of the same target tissue, which used the same technological intervention and demonstrated therapeutic efficacy and a low frequency of serious and life-threatening adverse events (e.g., <10%)

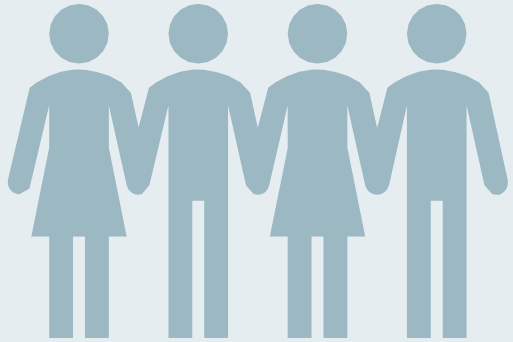


Deakin CT, Alexander IE, Hooker CA, Kerridge IH. Gene Therapy Researchers' Assessments of Risks and Perceptions of Risk Acceptability in Clinical Trials. *Molecular Therapy* 2013; 21(4): 806 – 15.

Human Genome Editing in the Clinic: New Challenges in Regulatory Benefit-Risk Assessment

Table 1. A Regulatory Perspective on Feasibility to Surmount Genome-Editing Safety and Efficacy Challenges

Challenges	Regulatory Feasibility to Overcome	Approaches to Address Challenges
Off-target activity, resulting in insertion or deletion mutations and/or chromosomal translocations	moderate	• assays to predict and identify off-target activity and/or translocations in place
		• biological assays to evaluate functional consequences of off-target activity still in development
Necessity to maximize efficiency of designer nuclease delivery and to control nuclease expression level and duration	moderate to high	• *in vivo* CRISPR-Cas delivery (mRNA, protein) via lipid nanoparticles may help to fine-tune level and duration of nuclease expression
		• *ex vivo* delivery of nuclease encoding mRNA by electroporation allows fine-tuning level and duration of nuclease expression
		• *ex vivo* delivery of nucleases in the form of DNA can be inefficient and induce high cytotoxicity
Inaccurate or random donor DNA (AAV or IDLVs, oligodeoxynucleotide donors) integration in the genome	moderate to high	• assays to detect random integration of AAV and IDLVs in place
		• randomly integrated oligodeoxynucleotides are difficult to detect
Highly variable tissue distribution of desired *in vivo* genome-editing event	moderate	• collection and assessment of a diverse panel of all major organs and tissues
Potential of immune reaction to nuclease components of current gene-editing systems	moderate	• use of immune suppression may be required



Abou-El-Enein M, Cathomen T, Ivics Z, June CH, Renner M, Schneider CK, Bauer G. Human Genome Editing in the Clinic: New Challenges in Regulatory Risk-Benefit Assessment. *Cell Stem Cell* 2017; 21: 427 – 30.

Informed Consent

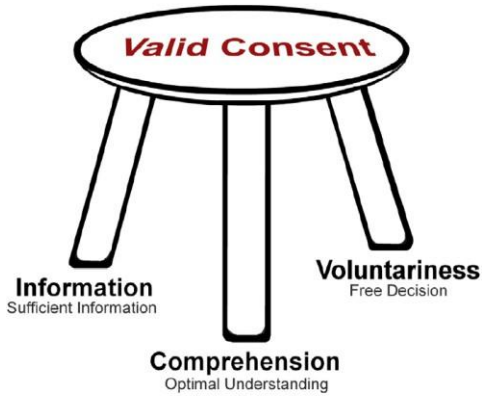


Fig 3. Informed consent.

Challenges in FIH include:

- Complexity of information to be disclosed
- Need to ascertain comprehension and voluntariness
- Uncertain nature of non-therapeutic design
- Participation of people considered "vulnerable"

Informed Consent Contents

The ICH GCP specifies that the following 20 issues should – if applicable – be properly addressed, using layman's language, in the written informed consent form. In short the 20 points are:

- *The trial involves research.*
- *Purpose of the trial.*
- *Trial treatment(s).*
- *Trial procedures.*
- *The participant's responsibilities.*
- *Experimental trial aspects.*
- *Foreseeable risks or inconveniences.*
- *Expected benefits.*
- *Alternative procedure(s) or treatment (s).*
- *Compensation and/or treatment available in the event of trial-related injury.*
- *Payment to participant.*
- *Expenses for participant.*
- *Participation is voluntary, and the participant may refuse to participate or withdraw from the trial at any time.*
- *The monitor(s), the auditor(s), the EC, and the regulatory authority(ies) will be granted direct access to the participant's medical records.*
- *Records identifying the participant will be kept confidential.*
- *The participant or representative will be informed if information becomes available that may be relevant to their willingness to continue participating in the trial.*
- *Person(s) to contact for further information regarding the trial, rights of trial participants, and in the event of trial-related injury.*
- *Circumstances and/or reasons under which participation in the trial may be terminated.*
- *Expected duration of trial participation.*
- *Approximate number of participants involved in the trial.*

Koonrungsesomboon N, Laothavorn J. Karbwang J. Ethical Considerations and Challenges in First-in-Human Research. *Translational Research* 2016; 177: 6 – 18.
Karlberg JPE, Speers MA. Reviewing Clinical Trials: A Guide for The Ethics Committee. 2010. 153 pages. Available at: https://books.google.com/books/about/Reviewing_Clinical_Trials.html?id=wGz2cQAACAAJ

Possible Challenges to Informed Consent

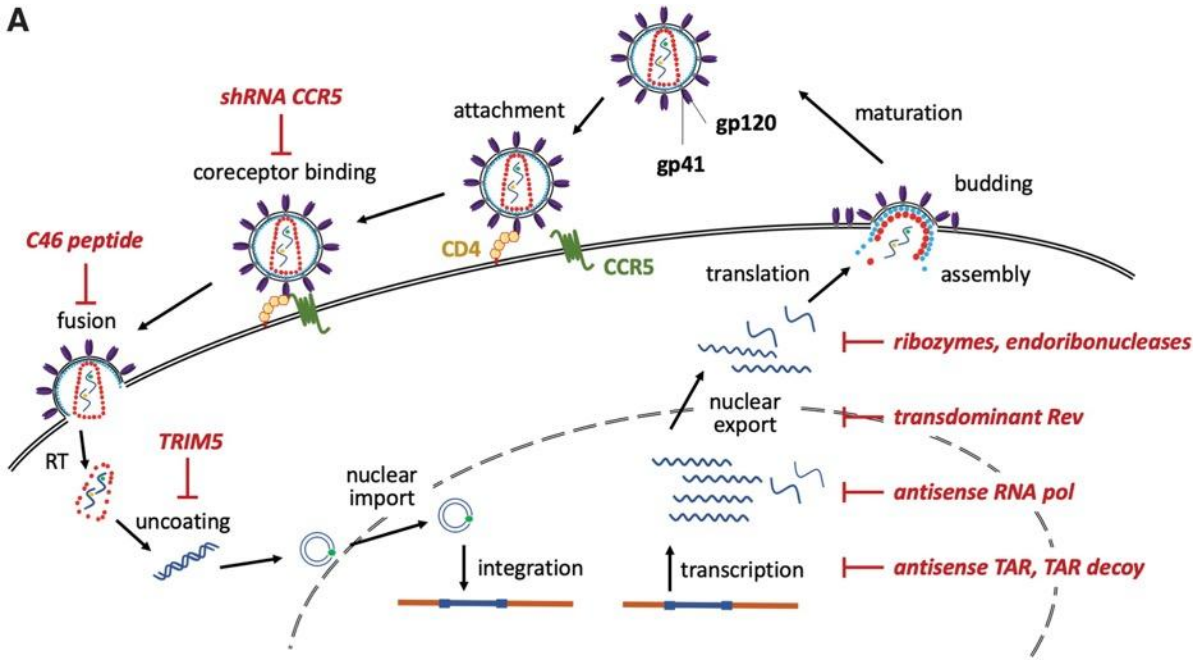
Table 1: Challenges during the informed consent process

Research team
Poor communication technique
Lack of time for the consent process
Inability to detect lack of patient comprehension
Legal outlook toward consent process
Patients
Anxiety and fear of new procedures
Health status (terminal, debilitating diseases)
Cognitive impairment (neurological disorders, elderly)
Denial of disease state
Informed consent document
Complex language
Medical terminologies
Legal nature
Lengthy consent documents

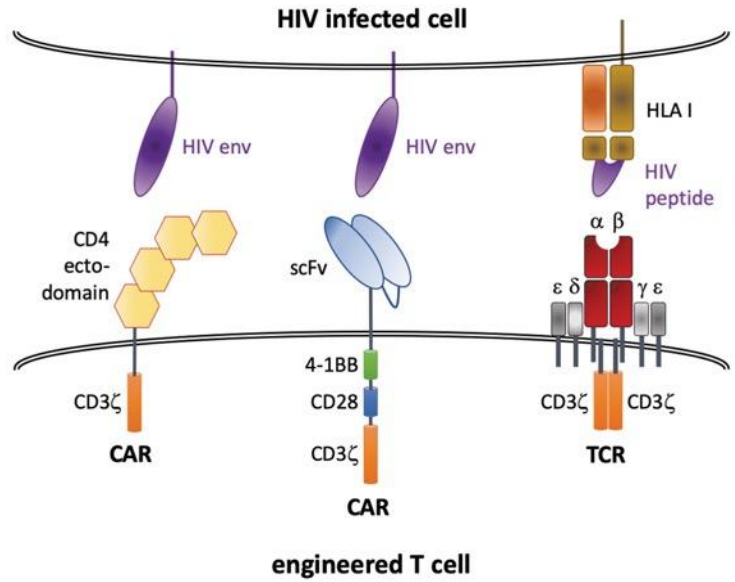
Kadam RA. Informed Consent Process: A Step Further Towards Making It Meaningful! *Perspectives in Clinical Research* 2017; 107 – 12.

Gene therapy strategies to treat HIV: Defensive, Offensive, Targeted

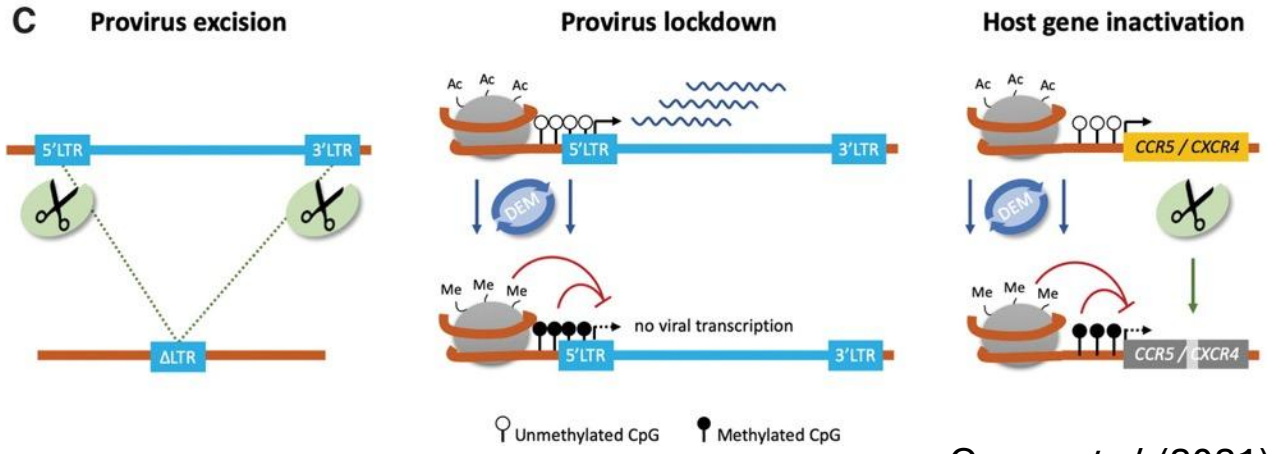
DEFENSIVE



OFFENSIVE



TARGETED



Cornu *et al.* (2021) Human Gene Therapy. 32(1-2):52-65

Selection of Suitable Population

- Addresses the principles of beneficence, justice and respect for persons
- Must be grounded on both scientific and ethical aspects
- Healthy volunteers generally preferred in FIH trials
  - Provide "cleanest" data and can tolerate adverse reactions better
  - But have more to lose
  - Not qualified to serve as participants in some studies that involve target-related, PD or surrogate parameters
- FDA issued policy in 1677 excluded women of child-bearing age in early-phase trials

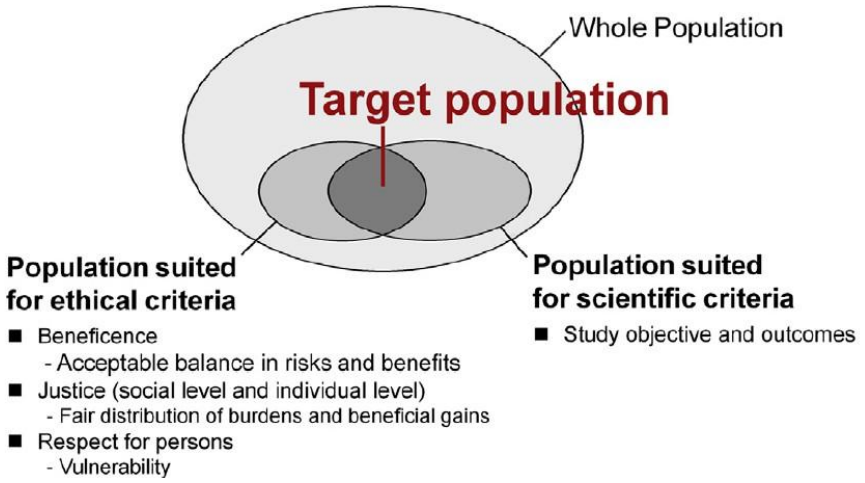


Fig 2. Subject selection.

J Law Med Ethics. 2009 Spring;37(1):38-50. doi: 10.1111/j.1748-720X.2009.00349.x.

First-in-human trial participants: not a vulnerable population, but vulnerable nonetheless

Rebecca Dresser [1]

Koonrungsesomboon N, Laothavorn J. Karbwang J. Ethical Considerations and Challenges in First-in-Human Research. *Translational Research* 2016; 177: 6 – 18.

Prevention of HIV Transmission during ATIs

A collaborative, multidisciplinary approach to HIV transmission risk mitigation during analytic treatment interruption

Partner protections in HIV cure-related trials involving analytical treatment interruption: Updated toolkit to mitigate HIV transmission risk

A partner protection package for HIV cure-related trials involving analytical treatment interruptions

Karine Dubé, Tia Morton, Lawrence Fox, Lynda Dee, David Palm, Thomas J Villa, William Freshwater, Jeff Taylor, Gail Graham, William B Carter, John A Sauceda, Michael J Peluso, Annette Rid

Call for justice-informed HIV cure trials with ATIs

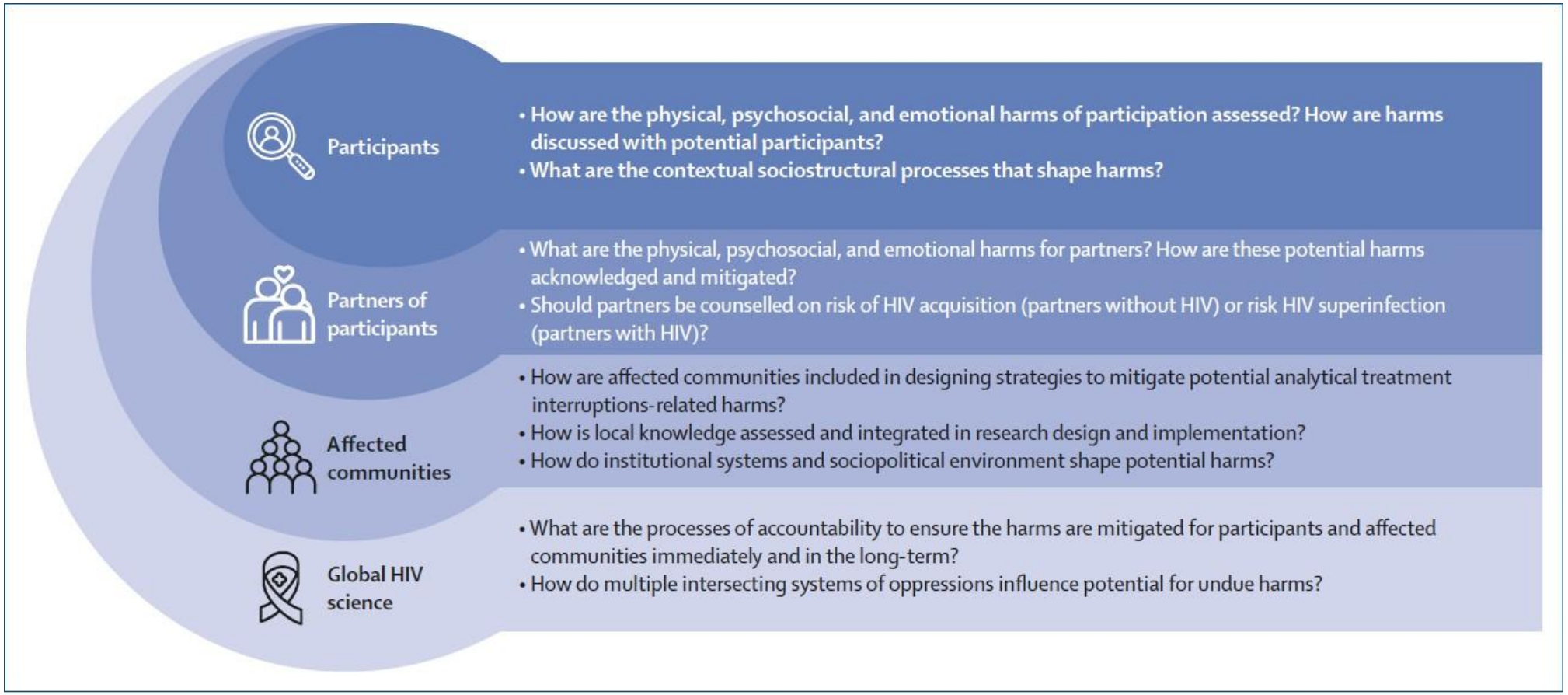


Figure: Key questions to mitigate potential harms related to HIV cure-related research with analytical treatment interruptions

Partner Dynamics

UCSF-amfAR Combination Trial

Participants and partners experienced difficulties during extended ATI:

- Partner protections more difficult as time progressed
- Discomfort with intimacy
- Difficulty finding out whether partners on PrEP
- One partner took emergency PEP, provoking anxiety and need for additional support
- Partners had fertility desires
  - Condomless sex coinciding with viremic window – quote

Need for more evidence-based BSSR in this area

> So, I'm dealing with the relationship piece, and then, a month of getting the test, and my partner is negative, and it's going to stay that way. The challenges in the relationship there, and then, navigating my body… It's been a real challenge for my partner during this journey, which I completely underestimated… I am in a relationship with a woman. And we have attempted to conceive during the time leading up to this… We were really arriving into this place where my partner is longing to try and conceive again. And that essentially requires unprotected sex… And that occurred right as I became detectable. So, once again, my partner had to go on to PrEP. She had to go through testing at that time, testing afterwards. It was a huge process for us and our relationship… It really affected our relationship, the trust piece. Essentially, I just had to take full ownership, like, "You're right. I should've said, 'No, we're not doing this right now.' But I didn't… The practicality and the realness began to subside the deep elements of hope or ego, or just blind ambition, and the realness started coming into effect. – Participant #03

Roles of REC, UNCST, and NDA

Research Ethics Committees (REC)

RECs review research protocols ensuring ethical standards and participant protection in biomedical research.

Uganda National Council for Science and Technology (UNCST)

UNCST provides national oversight, policy guidance, and registers research projects in Uganda.

National Drug Authority (NDA)

NDA regulates drug approvals and monitors biological products including advanced therapies.

Need for Policy Updates

Emerging cell and gene therapies require updated policies, specialized training, and enhanced collaboration.

Capacity 2023
EDCTP Grant

Presentation of the Technical Advisory Committee

Funded by
the European Union

Capacity 2023 Grant

- **Type of Action:** Horizon Europe Joint Undertaking Global Health EDCTP3 – Coordination and Support Action
- **Duration:** 36 months
- **Entry into force**: 1st April 2024– 31st March 2027
- **Requested grant amount:** EUR 999,313

Consortium

1 2 90 UNIVERSIDADE D COIMBRA

UNCST

JCRC Joint Clinical Research Centre

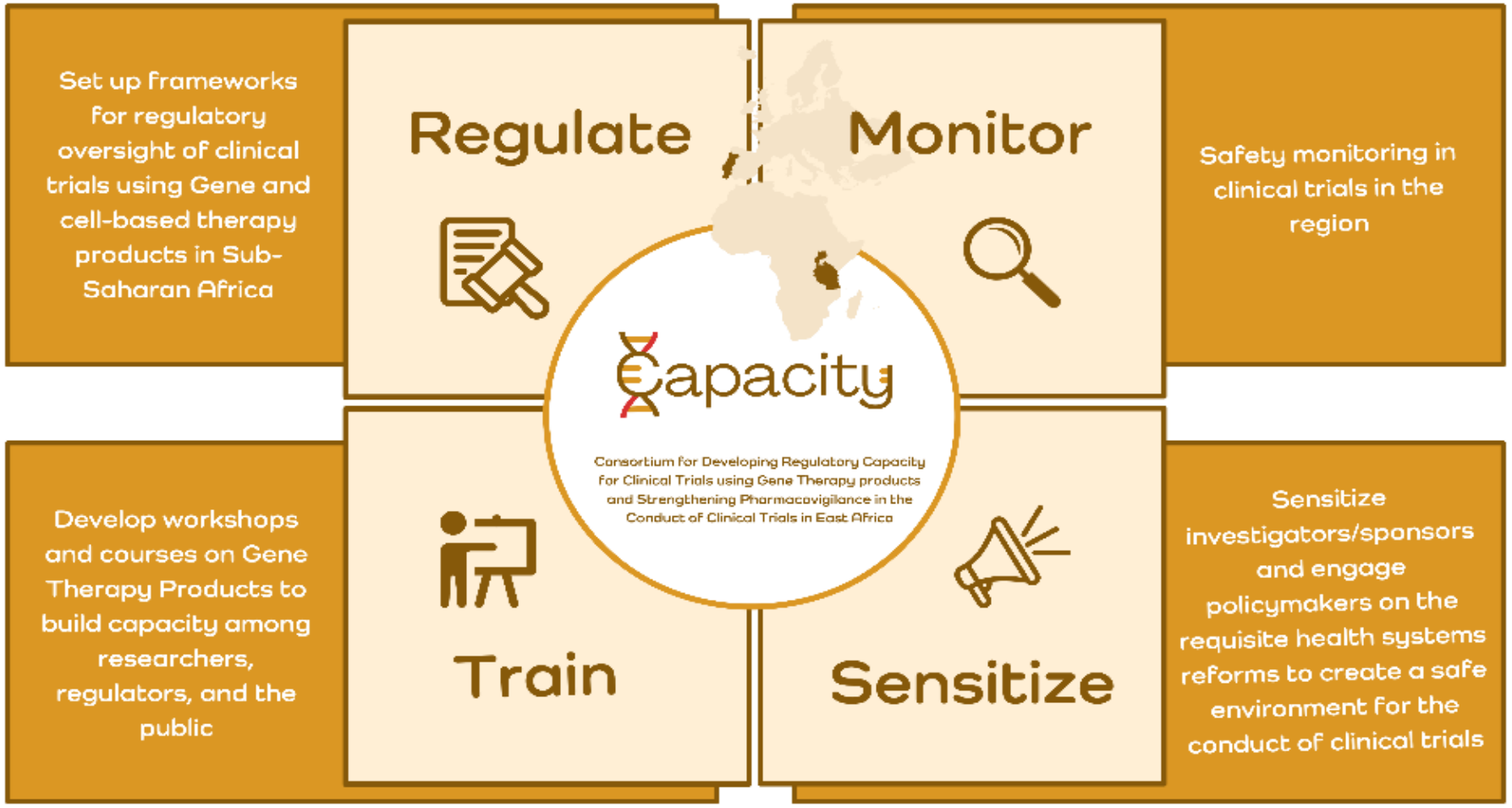
UGANDA NATIONAL DRUG AUTHORITY Safe Drugs Save Lives

MUHAS UNIVERSITY OF HEALTH AND ALLIED SCIENCES ELIMU TIBA UTAFITI

Global Health EDCTP3

"The project is funded by the Global Health EDCTP3 and The European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the EDCTP3. Neither the European Union nor the granting authority can be held responsible for them."

Overall Goals of the Grant



Capacity · Universidade de Coimbra · UNCST · JCRC Joint Clinical Research Centre · EDCTP3 · Funded by the European Union

Real-World Examples and Ethical Dilemmas

Informed Consent Challenges

Participants often struggle to understand scientific concepts, causing issues with obtaining proper informed consent.

Cultural and Community Engagement

Cultural beliefs and mistrust can hinder recruitment and retention in clinical trials, requiring sensitive community engagement.

Regulatory Oversight Limitations

Regulatory bodies sometimes lack expertise to evaluate novel therapies, leading to delays and inconsistent oversight.

Ethical Strategies for Research

Context-specific ethical strategies like tailored communication and capacity building improve research