CHANGEK

CHALLENGES AND INNOVATIVE CHANGES IN RESEARCH ETHICS REVIEWS

Review Guidelines on Gene Editing



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Executive Summary

In this deliverable, guidelines are presented for Research Ethics Committees (RECs), administrators, managers and research ethics officers on which organizations rely to review and oversee the ethical aspects of research, as well as to the researchers who design and carry out research studies. A core component of all contemporary research ethics guidelines is that research should be subject to prior ethical review by a competent REC to ensure that the ethical principles and practices put forward in guidelines and norms will be followed in the proposed research. Focused respectively on the relevant research ethics areas of gene editing, AI, electronic informed consent, and organoids, this task will provide guidance on the research ethics review process in these designated areas, will complement existing laws, regulations, and practices, and serve as a basis upon which RECs can develop their own specific practices, procedures and evaluations.

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1. Guideline 2: Gene editing

1.1. Introduction

Gene editing tools, especially technologies like CRISPR-Cas9 and its newer iterations, have transformed modern science and healthcare. By allowing scientists to precisely alter DNA sequences within living organisms, gene editing can be used to create novel therapeutics for previously incurable conditions (e.g. sickle cell anemia, Huntington's disease), prevent genetic conditions before birth, and offer a new method for tackling serious diseases (e.g. breast cancer, prostate cancer). Though gene editing has been used extensively in plants and animals, the use of gene editing in humans remains untested, complicated, and ambiguous. As a result, the novel prospect of editing the human genome brings a host of ethical dilemmas related to informed consent, safety, human enhancement, and more. Consequently, it becomes vital to balance the potential of gene editing with its ethical risks by championing ethical research practices and responsible governance.

1.1.1. Role of RECs for ethical development of Gene Editing

Research ethics committees (RECs) play a crucial role in guiding the responsible development and application of human gene editing technologies. While Regulation 536/2014 distinguishes ethical review from scientific evaluation, RECs are nonetheless responsible for considering aspects of scientific validity that directly affect participant protection. They do not duplicate the full scientific assessment conducted by competent authorities, but they assess whether the study design is sufficiently robust to justify exposing participants to risk. For example, RECs may scrutinize first-in-human gene editing studies for inadequate preclinical evidence, poorly defined endpoints, disproportionate risk–benefit ratios, or insufficiently justified patient selection. In this way, RECs ensure that ethical standards are upheld, participants' rights are protected, and potential harms are minimized. As gene editing moves closer to clinical application, this oversight becomes even more essential, ensuring that the pursuit of genetic advancement does not outpace the ethical frameworks needed to guide it.

1.2. Background and Context: Gene Editing

Before discussing the ethical issues and guidelines involved with the various types and uses of gene editing, it is important to establish the fundamental and contextual details associated with how gene editing works as well as to differentiate the types of editing that are possible with recent gene editing systems. The following sections will highlight the context behind various recent and historical gene editing tools as well as explain the scientific function of these tools for various human applications.

1.2.1. Scientific and Historical Background of GE

Gene editing refers to the method that allows scientists to make precise changes to the DNA of living organisms, such as plants, bacteria, animals, and humans, to change physical attributes, genetic variants increasing disease risk, and genetic sources of severe conditions. (1) This concept has been a part of scientific discovery and can be traced back to the 1970s with the first efforts toward recombinant DNA technology, but the field advanced dramatically after certain key discoveries. (2) First, the field boomed exponentially after the development of zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) in the early 2000s.(3)(4) Both of these tools allowed researchers to make double-stranded breaks at specific locations in DNA, which could then be repaired in a way that altered the genomic sequence. Both these methods, however, are complex, burdensome approaches that are also often expensive to design, which does not make them the ideal gene editing system for widespread use.(5)

The field expanded again in 2012 with the discovery of CRISPR-Cas9, a powerful yet simple gene editing system adapted from a bacterial natural defense mechanism.(6) CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, uses a guide RNA (gRNA), synthetic molecule that matches to a desired location in the genome, to direct the Cas enzyme to a specific part of the DNA sequence and make a precise cut in the DNA. (7)The cell then attempts to repair the break, allowing scientists to disable a gene, fix a mutation, or insert new genetic material. (7) CRISPR is set apart from some of the older gene editing tools because it bypasses those models' labor-intensive protein engineering required to reach a DNA target location, whereas CRISPR just needs the generation of a new gRNA.(8) As a result, it is significantly more accessible, efficient, precise, and cost-effective.

In fact, newer iterations of CRISPR are constantly being patented. For instance, highly precise base editing allows scientists to change a single DNA base without even cutting the DNA strand, significantly lowering the risk of errors that may occur during DNA repair.(9) Similarly, prime editing enables even more accurate edits, including gene insertions and deletions for large swaths of DNA similarly without making double-stranded DNA breaks.(10) These advances have made gene editing safer and more precise, especially for human applications, which has sparked a recent explosion in therapeutics research and human health studies. However, it is also important to note that the rise of CRISPR technology has also sparked intense legal battles over intellectual property rights over these tools as it affects researchers' access to innovation and works counter to open science practices.(11)

1.2.2. Types of GE and Therapeutic Uses for GE Tools

The key distinction when considering gene editing is between somatic gene editing and germline (or heritable) gene editing, which present vastly different consequences and ethical dilemmas. Somatic gene editing is a type of gene editing where the DNA changes are made only to somatic cells, or the body's tissues.(12) The changes are not passed on to future generations and only affect the individual being treated.(12) This type of editing is typically used as medical treatment for various diseases, such as cancers and genetic disorders since the goal is only to alter the DNA within affected tissues or organs.(12) As a result, a lot of the ethical discussion focuses on the safety and efficacy of such an intervention.

Germline gene editing involves making changes to the DNA in reproductive cells and tissue, such as eggs, sperms, embryos, and zygotes.(13) Changes to these cells are intended to be passed on to future generations, which holds potential for eliminating genetic diseases before birth as well as permanently within a genetic line.(13) However, this type of editing raises many incredibly complex ethical and societal issues about the potential for dangerous human enhancements, long-term, unintended consequences, and permanent changes to the human gene pool.(14) As a result, germline editing remains a controversial topic globally due to its profound implications for human evolution and identity and has been prohibited in many countries.

Translating editing tools into practically usable treatments, also known as a gene editing therapeutics, is a complex process.(15) First, scientists use known genomic information about diseases to identify a faulty gene. Then, they must design a precise gRNA and editing strategy (e.g. gene insertion or deletion) and, finally, safely deliver it to the right cells without causing side effects like toxicity, immune reactions, or off-target edits.(15) Diseases caused by a single gene, such as cystic fibrosis, are more straightforward targets, but many conditions involve multiple genes or variants, complicating therapeutic development.(16) Additional challenges include precision, which is crucial to ensure that the therapeutic creates accurate changes in the right part of the body.(17) Delivery also remains a major hurdle, with viral vectors and lipid nanoparticles being common methods for transporting editing tools into cells.(17)

Gene editing therapies are also categorized as in vivo, where the editing tools are delivered directly into the body, and ex vivo, where cells are extracted, edited outside the body, and transplanted.(18) Ex vivo approaches offer greater control and have already shown clinical promise but can be very demanding with their many steps.(19) For instance, Casgevy is the first approved CRISPR-based one-time therapy for sickle cell disease and beta-thalassemia and uses an ex vivo model.(19) However, in vivo approaches may offer greater cost-effectiveness and broader applicability for more types of diseases.(20) While much of the current focus is on treating inherited genetic disorders, gene editing also holds potential for tackling cancer, viral infections like HIV, and other complex diseases. However, these advancements come with significant challenges, including ensuring safety, minimizing off-target effects, and addressing ethical concerns such as informed consent and fair access.(21) Moving forward, careful oversight, strong regulation, and collaboration across stakeholders will be essential for the responsible use of these powerful technologies.

1.3. Germline Gene Editing (GGE): Clinical and Research Uses

Because germline gene editing (GGE) is a high-risk and ethically complicated endeavor (as highlighted above), the permissibility of GGE is determined by whether it is being conducted for research purposes or as a clinical intervention. Currently, clinical uses of GGE are strictly forbidden; however, research uses of GGE are often vague and determined on a national basis.

1.3.1. Legal landscape for clinical applications

Current laws and regulations surrounding germline editing are largely straightforward in that they consider the clinical use of germline gene editing to be illegal at this time. A key international document reinforcing this position is the Convention on Human Rights and Biomedicine, also known as the Oviedo Convention (22) which addresses both clinical and research uses of gene editing. Article 13 of the Convention permits interventions on the human genome only for preventive, diagnostic, or therapeutic purposes, and explicitly prohibits modifications that would affect future generations. While the Convention allows for somatic gene editing, it clearly bans germline interventions. However, it's important to note that not all European countries have ratified the Oviedo Convention, so its provisions are not universally binding across the continent. In addition to these international guidelines, many countries have also enacted their own national bans on the clinical use of GGE.

Additionally, the EU clinical trials regulation (23) further restricts germline editing. Article 90 of the regulation states that gene therapy clinical trials must not result in changes to an individual's germline genetic identity, reinforcing a strong stance against heritable editing. Furthermore, professional societies, including the European Society of Human Genetics and the European Society of Human Reproduction and Embryology, also oppose the clinical use of germline editing, deeming it premature and unacceptable at this time (24). Additionally, the World Health Organization (WHO) supports a temporary ban on germline editing for reproductive purposes, citing concerns about safety, inequality, human dignity, and insufficient long-term data. They also highlight the importance of continued international discussion before any clinical use of germline editing can be considered (25).

1.3.2. He Jiankui Experiment: Impacts of clinical research involving GGE

The sheer ethical complexities of clinical research involving GGE were brought into the limelight of the scientific community in 2018 when scientist He Jiankui announced that he had used CRISPR-Cas9 to modify the genomes of twin girls.(26) He altered their CCR5 genes in an attempt to confer resistance to HIV, marking the first known case of clinical germline genome editing in humans.(27) He presented his experiment at the second World Summit on Human Gene Editing and was swiftly met with strong backlash from the scientific community.(26) In fact, researchers, scientific institutions, and national governments across the globe condemned his experiment, labeling He as a rogue scientist, extremely irresponsible, and in clear violation of regulatory and medical ethics standards. In addition to this ethical condemnation, He faced legal consequences: Chinese authorities investigated his work, and in 2019 he was sentenced to three years in prison and fined for conducting

illegal medical practices, highlighting that clinical germline genome editing can carry both ethical and legal repercussions (28) .

1.3.2.1. Research Ethics Considerations for clinical research involving GGE

Firstly, He's experiment was not only a sharp wake-up call for scientists globally, but this case can be used to highlight serious research ethics concerns and missteps with clinical uses of germline gene editing. For instance, the safety and efficacy of germline intervention is widely considered to be unclear. Though gene editing techniques have improved significantly, especially with the advent of CRISPR editing tools, risks of the intervention are still high (e.g. off-target effects or unintended mutations) and still require considerable additional research.(26) Furthermore, there is not sufficient documentation about the CCR5 gene to be able to adequately claim that modifying it could lead to a long-term health benefit.(26) He also did not present sufficient pre-clinical evidence to prove the safety of the intervention.(26)

Secondly, the clinical utility of genetic interventions must be clear and provide a sufficiently compelling reason to take on the risks involved with germline editing. This was not achieved in He's experiment since HIV transmission to future offspring can be easily and effectively prevented through alternative methods, such as Assistive Reproductive Technology.(26) Additionally, some argue that GGE itself does not offer greater medical benefit over other reproductive technologies since it can also be used negatively for human enhancement, which is widely understood to be impermissible. For instance, severe diseases can also be avoided using in-vitro fertilization in conjunction with preimplantation genetic diagnosis, prenatal testing, sperm donors, somatic gene therapies, or adoption.(29)

Thirdly, the long-term effects of GGE are still unclear, further proving this experiment violated key research ethics standards. Currently, there is little to no understanding of the long-term consequences of germline editing, not just on the individual receiving the intervention but in the human gene pool as well.(29) This is further complicated because there are no clear distinctions yet about when GGE is being used as a therapeutic medical intervention or as human enhancement, which requires further and more extensive studies.(29)

Fourthly, there is still no broad, societal consensus on the moral impacts of GGE, since altering the genome can be considered altering a fundamental aspect of humanity.(29) Further discussions, including a wide range of voices, should have been established before He Jiankui's experiment.

Finally, one of the repercussions of He Jiankui's experiment on germline genome editing (GGE) was a call for a global moratorium. In 2019, leading scientists published a proposal in Nature advocating for a temporary halt of at least five years on clinical germline genome editing, pending the development of clearer scientific, ethical, and regulatory standards. Although this proposal was not legally binding, it significantly influenced international governance discussions. Since then, organizations such as the World Health Organization have issued recommendations aimed at strengthening oversight and discouraging premature clinical use. As of 2026, no international consensus has emerged in favor of permitting clinical germline genome editing, and many jurisdictions continue to prohibit or strictly

limit such applications. The moratorium has thus functioned less as a formal ban and more as a normative framework shaping ongoing regulatory and ethical deliberations.

1.3.3. Research Ethics Standards for Research Applications of GGE

Research considerations involving germline gene editing (GGE) are often vague and confusing because the legality of GGE research varies widely across countries.(30) Some nations, such as the UK and Belgium, explicitly permit germline gene editing solely for research purposes and is codified through national policy.(30) However, countries, such as Germany and Austria, explicitly prohibit germline genome editing for research.(30) Other countries, such as Sweden and Norway, allow the research but in specified and controlled circumstances. Many more countries, especially within the EU, often have vague or indeterminate stances on GGE research.(30) This is further confused since international laws, such as the Oviedo Convention, do not provide explicit guidance on the legality of GGE research. The lack of a unified international framework also raises concerns about "ethics dumping," where researchers may seek more permissive jurisdictions to conduct controversial work, undermining global responsible and transparent research.(30)

The regulatory landscape of germline genome editing research cannot be understood independently from embryo research regulation. Because heritable genome editing typically involves the modification of human embryos at early stages of development, national laws governing embryo research directly shape the permissibility and scope of GGE research. Globally, embryo research frameworks vary significantly and reflect diverse cultural, religious, and ethical traditions. Germline gene editing is closely linked to embryonic research because editing heritable DNA typically involves modifying embryos at many stages of development. Broadly, there are two principles followed when conducting research involving embryos.(31) The first is to ensure edited embryos for research are not implanted in any human patients for investigative purposes.(31) The second is the widely accepted 14-day rule that states embryos are not allowed to be cultured beyond 14 days (in countries that allows research on embryos) since it marks the beginning stages of individual development of embryos.(32) However, some researchers are calling for the extension of this rule to at least 28 days to allow for more extensive studies.(32)

Despite the confusion surrounding germline gene editing research, there are still long-standing research ethics principles that can guide the future applications of GGE in research. For instance, since germline gene editing would require tissue donation (e.g. embryonic or fetal tissue), adequate consent must be obtained from donors, ensuring they fully understand the nature, purpose, and potential implications of the research.(33) Additionally, measures must be taken to ensure donors' privacy as well, especially if their genetic data is made public at any time, Moreover, guidance on research values have been provided by the World Health Organization in 2021. They emphasized that GGE must be guided by ethical values such as promoting well-being, transparency, due care, responsible science, respect for persons, and fairness. In its 2021 recommendations, the WHO called for strong global oversight, including an international registry for genome editing research and mechanisms to prevent unethical or unsafe practices.(34) As scientific capabilities advance, there are increasing calls for robust oversight frameworks, not only to govern research but also to guide the potential clinical application of these technologies in a responsible and equitable manner.

1.3.4. Looking towards the future

As germline gene editing continues to evolve, research ethics guidelines and legal frameworks surrounding its use are undergoing dynamic and ongoing revision. With the rapid advancement of basic scientific research and increased public and professional discourse, there is growing recognition of both the potential benefits and profound ethical implications of altering the human germline. These discussions are prompting policymakers, ethicists, and scientists to continuously reassess existing standards, ensuring they reflect current scientific capabilities, societal values, and ethical considerations. As a result, the regulatory landscape for germline editing remains fluid, with laws and guidelines being updated or newly developed in response to emerging research, evolving norms, and shifting public attitudes. However, at this time, many researchers have implicitly agreed to extend the moratorium beyond 2024 as the technology has not reached a point where it can safely be used in humans.

1.3.5. Recommendations

- RECs should ensure that proposals explicitly state whether the GGE is intended for research or clinical application, as the ethical and legal implications differ significantly. RECs should reject proposals involving clinical germline genome editing, in line with current international and national prohibitions, including the Oviedo Convention and applicable EU regulations.
- RECs should require clarification as to whether the use of embryos for GGE will result in their destruction, particularly where national legislation prohibits such practices or where funding bodies, such as the European Commission, restrict funding for research involving embryo destruction.
- RECs should confirm that proposed GGE research is legally permissible in the country where it will be conducted and does not circumvent national or international bans. They should scrutinize cross-border research arrangements to prevent “ethics dumping” into more permissive jurisdictions.
- RECs should require comprehensive and understandable consent forms from all tissue donors (including embryonic or fetal tissue donors), clearly disclosing the research purpose, risks, and broader implications. They should also ensure appropriate safeguards for genetic data privacy.
- RECs should ensure compliance with the 14-day limit on embryo research, unless otherwise lawfully justified under evolving ethical guidelines, and should enforce a strict prohibition on implantation of genetically edited embryos in human subjects.
- In jurisdictions permitting GGE research, RECs should assess whether proposed modifications are ethically justifiable, for example where they target serious genetic diseases for which no alternative treatments exist.

1.4. Somatic Gene Editing

Somatic gene editing holds immense potential to transform medicine by precisely correcting disease-causing mutations, offering targeted, long-lasting treatments for a wide range of conditions (e.g. sickle cell disease, cystic fibrosis, and muscular dystrophy). (35) Beyond monogenic disorders, it also shows promise in enhancing cancer therapies, engineering immune cells, and combating viral infections like HIV.(36) However, this form of gene editing presents many research ethics concerns as an emerging therapy with both high potential and high risks. Because it involves altering genes in non-reproductive cells, it requires rigorous ethical oversight to ensure that interventions are scientifically valid, and participants are adequately protected during clinical trials. At this time, there is only one gene-editing therapeutic that has been approved (Casgevy).(37) However, many more similar therapeutics are in various stages of the clinical pipeline, making ethics considerations increasingly urgent to ensure that safety, informed consent, equitable access, and long-term oversight are prioritized as the field rapidly evolves.(38)

Research using gene editing technologies, particularly in non-clinical and preclinical settings, is now well-established, with robust protocols and regulatory oversight guiding laboratory-based studies around the world. As such, in the following sections, this guidance document will be describing the key research ethics concerns related to somatic gene editing in clinical settings as well as potential recommendations for RECs to effectively ensure safe and ethical use of these therapeutics in clinical trials and research experiments. It is not the intention to provide an exhaustive list of issues to consider, but to provide an overview of the most important considerations for ethics committees.

1.4.1. Scientific and safety risks caused by somatic editing

Though gene editing offers immense potential for treating genetic disorders and advancing medicine, it also poses significant safety risks that warrant careful consideration. One such safety concern is the risk of off-target effects if gene editing tools unintentionally edit the wrong cells or a wrong section of DNA resulting in harmful mutations or disrupted gene function.(14) In certain cases, the gene edits could unintentionally activate cancer-related genes, or oncogenes, or disrupt tumor suppressor genes, which could lead to uncontrolled cell growth and malignancies known as oncogenic events.(39) Similarly, there is also a risk of mosaicism, which occurs if the gene editing intervention only successfully edits a portion of the target cells, which could create inconsistent treatment results or low efficiency of treatment.(40) Moreover, these safety risks are often irreversible due to the permanent nature of gene editing, making thorough risk assessment even more critical. Broadly, the long-term effects of gene edits as a treatment are not properly understood yet, making it difficult to accurately predict both the potential benefits and consequences of gene editing therapeutics.(41)

However, these risks only encompass concerns related to gene editing itself. A gene editing therapeutic presents additional risks if the delivery vector (typically a viral vector) triggers a patient's immune system or causes infection.(42) Additionally, delivery mechanisms can contribute to insertional mutagenesis, a process in which the inserted genetic material disrupts normal cellular function by integrating into unintended sites within the genome. This risk is particularly associated with integrating viral vectors, such as retroviruses or lentiviruses, which may insert near or within oncogenes or tumor suppressor genes, potentially leading to malignancy.(43) Non-viral methods,

such as lipid nanoparticles or electroporation, may also cause cellular stress, membrane damage, or inflammatory reactions.(44)

To help prevent safety risks associated with gene editing therapies, several key strategies must be implemented across all stages of clinical development. These strategies broadly aim to prevent gene editing's safety concerns with thorough preparation or detect emerging risks early, allowing for timely intervention and mitigation should adverse effects arise. Foremost, extensive preclinical studies using the relevant cellular and animal models are essential to demonstrate that the therapeutic is effective at treating its target condition but also has a low frequency of safety risks, such as off-target effects, insertional mutagenesis, or immune reactions. These studies should incorporate comprehensive genomic analyses to assess potential unintended edits or structural variations. Additionally, during clinical trials, continuous monitoring and transparent reporting of results are crucial to promptly identify and respond to emerging risks. This is especially true for severe adverse events, such as sudden death, which may necessitate the early termination of a trial. Furthermore, reporting should include not only routine safety assessments but also deeper molecular profiling of patient samples when possible. Finally, long-term follow-up after the completion of a clinical trial is vital, as some complications, such as delayed oncogenesis or immune-related effects, may not manifest for years. By integrating robust preclinical evidence, vigilant clinical monitoring, and extended post-trial surveillance, gene editing therapeutic research can more responsibly advance from bench to bedside while prioritizing patient safety. Furthermore, it is important to create stricter standards, practices, and considerations for gene editing trials involving vulnerable pediatric populations.

REC's play an important role in assessing the ethical acceptability of gene editing trials, including the adequacy of the supporting preclinical evidence. While RECs do not duplicate the full scientific evaluation conducted by competent authorities, they must consider whether the available preclinical data are sufficiently robust to justify exposing participants to potential risks. For example, REC members may examine whether relevant animal models demonstrate acceptable safety profiles, whether off-target effects have been adequately assessed, whether dose-escalation strategies are justified, and whether long-term toxicity risks have been reasonably addressed. In first-in-human gene editing trials, particular attention may be given to the strength and reproducibility of preclinical findings and the plausibility of the proposed therapeutic mechanism.

REC members also evaluate whether the study design includes appropriate risk-minimization strategies and long-term monitoring plans, and whether the anticipated benefits reasonably outweigh the foreseeable risks. In addition, they assess the adequacy of the informed consent process, ensuring that participants understand the experimental and potentially irreversible nature of gene editing interventions. Although RECs are primarily involved in the initial ethical review and approval of research projects and do not conduct ongoing trial monitoring themselves, they may require periodic safety reports and review substantial protocol amendments during the course of the study.

Research Ethics Committee (REC) members are responsible not only for ensuring that clinical trials are ethically sound and safe for participants, but also for verifying that studies comply with all relevant (local) national laws, regulations, and ethics codes. This is particularly important in gene editing trials, where legal and ethical standards can vary widely between countries. As such, REC members should be well-informed about their country's specific regulations on gene editing, which are often published by national drug regulatory authorities, as well as additional laws related to data protection, patient rights, and biosafety. By staying up to date with these legal frameworks, REC members help ensure that clinical trials are both ethically and legally compliant, safeguarding participants and supporting responsible research conduct.

In vivo and ex vivo gene editing therapies carry differing safety and logistical considerations, mainly due to differences in how they are processed and delivered. In vivo therapies involve delivering gene editing tools directly into the patient's body, such as through intravenous infusion or localized injection.(45) This method is generally less invasive and more patient-friendly since it avoids the need for surgical procedures or cell extraction. The single-step nature of in vivo editing reduces manufacturing complexity and time as well as potentially lowering costs.(46) Additionally, because it does not rely on personalized cell manipulation, in vivo therapy may become more scalable and, thus, more accessible for more patients to receive potentially life-saving care.(46) It also offers the advantage of targeting a wider range of organs, such as the liver, brain, or muscle, broadening its therapeutic applications.(45) However, it is not without potential risks. The direct delivery of gene editing agents throughout the body raises concerns about off-target effects, immune reactions, and unintended edits in non-target tissues, which can be harder to control than in ex vivo settings.

In contrast, ex vivo gene editing involves removing a patient's cells, editing them in a laboratory, and then reintroducing them into the body.(46) This process allows for more precise control and verification of the edits before the cells are returned, which can reduce some risks of unintended outcomes. However, the procedure itself introduces additional burdens. Patients must undergo chemotherapy or radiation to prepare their bodies for the edited cells, which can cause serious side effects such as immune suppression, organ damage, and infection.(47) The process of cell extraction and transplantation is also painful, time-consuming, and carries risks like graft failure or infection.(48) Furthermore, ex vivo therapies require specialized cell processing facilities and expert personnel, making them significantly more expensive and limiting their availability to well-resourced medical centers. As a result, while ex vivo therapies may offer greater control, their complexity and invasiveness pose additional safety and accessibility challenges compared to in vivo approaches that REC members should consider.(49)

1.4.2. Concerns Involved with Patient Recruitment in Trials

Patient recruitment for clinical trials involving gene editing therapeutics presents a distinct set of ethical and logistical challenges. One of the primary concerns is the vulnerability of the patient population. Many gene editing interventions target severe, life-threatening, or rare genetic conditions (often monogenic in nature) for which there are few existing treatments or often no adequate treatment at all.(50) As a result, patients and families affected by these conditions may face greater pressures to enroll in a study, which can compromise the voluntariness of given consent

and their decision-making autonomy.(51) Although the severity of a condition may create urgency for intervention, it does not ethically permit compromising participant safety. Efforts must be taken to ensure the fairness of the study and prevent exploitation, through what are known as collateral affective benefits, or feelings of hope or altruism that may motivate individuals to participate.(51) These emotions, though genuine, can cloud judgment and make it harder for patients to fully weigh the risks. Researchers must prioritize the well-being and rights of current patients over speculative benefits for others in the future.

However, another complexity unique to gene editing trials is the absence of a healthy volunteer population in early-phase research. Unlike traditional clinical trials that often begin with healthy subjects to evaluate safety and dosage, gene editing trials typically involve only patients with the targeted condition. This is true for a couple of reasons, such as the lack of direct benefit of a gene editing intervention for healthy volunteers, high risks of unnecessary and irreversible invasive interventions, and the targeted nature of the therapy for correcting disease-causing genes that do not exist in healthy patient populations. This raises challenges in both designing fair recruitment protocols and ensuring equitable access to the trial. Furthermore, because of the high stakes involved and the scarcity of eligible participants, maintaining fairness and avoiding undue inducement or exploitation becomes a critical concern. Such pressure often occurs when the promise of a potentially life-saving therapy exerts strong emotional or psychological pressure on patients, leading them to participate without fully considering the risks or alternatives.

REC members play an important role in ensuring fair patient recruitment though they are not directly in charge of patient recruitment. Instead, a REC member will review the recruitment procedures and materials to ensure that they are both ethical and fair to potential trial participants. For instance, compensation for participants in gene editing clinical trials should be fair, reflecting the time, effort, and potential burdens involved, without being so high as to unduly influence or pressure individuals into participating. As such, it is important for a REC member to assess the voluntariness and vulnerability of participants, especially for rare conditions, and that they are adequately informed of the potential risks and irreversible outcomes of gene editing in humans. Additionally, REC members should mandate independent patient support, where independent patient advocates or ethics consultants are available to help participants understand the study to help safeguard patient autonomy. This would also include reviewing communication material, such as informational brochures and recruitment messages, to prevent misleading language or overpromising of benefits. Finally, RECs should require researchers to communicate clearly about post-trial care and access to treatment (if it is still needed after the gene editing intervention) as well as how results will be shared with participants. If there are cases where RECs are involved in any ongoing ethical re-evaluation of studies, they should ensure that consent is an ongoing process and that participants have access to education, information, and the trial researchers both during and after the study.

1.4.3. Informed Consent and Therapeutic Misconception in Trials

These recruitment challenges can give rise to ethical pitfalls during first-in-human trials, such as therapeutic misconception, where participants mistakenly believe the primary purpose of the trial is to provide treatment rather than to conduct scientific investigation, such as to determine if there are any dosage related concerns (too high or too low) or toxicity effects of the intervention.(52) Thus, participants may mistakenly believe they are receiving personalized treatment rather than contributing to an experimental study. This can also be compounded by the placebo effect, where participants experience perceived or real improvements in their condition simply due to the belief that they are receiving an effective therapy. This effect can be particularly strong in trials involving severe or rare genetic disorders, where patients may feel hopeful or emotionally invested in the outcome.(51) Addressing these challenges requires robust informed consent procedures and a strong commitment to upholding patient autonomy throughout the recruitment and trial process, which involves effective evaluation from RECs.

The researcher's purpose should be to uphold key ethical principles that ensure the safety, dignity, and rights of participants throughout the trial process. Independence is a foundational principle, achieved through oversight by ethics review committees (RECs), institutional review boards (IRBs), or data safety monitoring boards (DSMBs) who serve to review and evaluate the study's design, ethical implications, and progress.(53) (54) (55)These bodies help ensure that the research adheres to established ethical standards and that potential risks to participants are minimized. Transparency is equally crucial since transparent reporting of both positive and negative outcomes, as well as long-term follow-up data, fosters trust and allows for the replication and critical evaluation of findings.(56) Lastly, accountability demands that all parties involved in the research, such as investigators, sponsors, and physicians, take full responsibility for the well-being of participants.(56) This includes ensuring that patients are adequately informed about risks, providing appropriate care during the trial, and ensuring that participants' rights are protected. These include the patients' right to be continuously informed about the progress of the treatment, the right to ask questions about the study, the right to privacy and data confidentiality, the right to withdraw from the study, the right to medical care if the procedure is harmful or has unanticipated effects, and the right to receive fair compensation for the trial. Through these ethical commitments, researchers can safeguard the integrity of the research process while respecting and protecting the rights of those who participate in these studies.

Informed consent in gene editing trials should be especially robust, focusing on fostering realistic expectations and ensuring patients are fully informed about available alternatives before participating in a clinical trial. This involves educating participants clearly and thoroughly about the experimental nature of the therapy, its risks and benefits, and what other options exist.(57) Effective strategies include tailoring consent procedures to the patient's level of understanding, recognizing and respecting their values such as altruism or a desire for empowerment, and engaging both patients and their caregivers in the co-development of study protocols. Open discussions about potential side effects, expected quality of life, and clearly outlining the stages at which withdrawal from the trial is possible are also crucial to ethical engagement.(57) Additionally, safeguards must be

in place to prevent undue influence from physicians, who may unintentionally pressure patients due to their roles and perceptions as authority figures. When conducting clinical trials involving a pediatric population, ethical considerations become even more complex due to the inherent vulnerability of children. Informed consent procedures must be adapted to account for the fact that minors cannot provide full consent on their own, requiring both parental or guardian consent and, when appropriate, the child's assent.(58) Pediatric trials also raise unique concerns related to independence, as the power dynamics between researchers, parents, and healthcare providers can create pressures that might unduly influence the child's or parent's decision to participate.(58) Transparency remains just as critical, but it must be carefully tailored to avoid overwhelming parents or guardians with complex scientific information, focusing instead on clear and accessible explanations of what participation in the trial entails.. Furthermore, ethical review processes, including oversight by RECs and IRBs, must consider the unique needs of pediatric populations, ensuring that any risk is minimized and that potential benefits are in the best interest of the child. In pediatric trials, the focus should be on safeguarding the well-being of children, ensuring that their participation is in line with their best interests, while also considering the potential for long-term impacts on their development and health.(58)

In the context of RECs, members play a vital role in ensuring that before being enrolled in gene editing clinical trials, participants, especially those from vulnerable populations (rare disease communities, pediatric populations, or marginalized groups), must be adequately informed , in order for consent to be specific, informed, unambiguous and freely given. This includes informing participants about all safety risks (short- and long-term) and taking additional measures to dispel potential therapeutic misconceptions. Because these trials often involve patients with severe or untreatable conditions, RECs must closely evaluate how consent materials and processes are designed and delivered as their role is to make sure that participants fully understand the experimental nature of the intervention. RECs ensure that consent forms clearly explain the goals of the trial, the distinction between care and research, all available alternatives to participation, they may also require that information is tailored to participants' comprehension levels and that extra protections are in place for vulnerable populations, such as independent patient advocates or opportunities for patients to discuss their decision outside the influence of clinical investigators. This also underscores the importance of long-term oversight mechanisms. While RECs do not themselves conduct follow-up studies or track real-world outcomes, they play a role in ensuring that appropriate long-term monitoring plans are incorporated into the study design. RECs may require researchers to include post-trial follow-up protocols, safety reporting obligations, and procedures for communicating new risk information to participants. Through continuing review and evaluation of protocol amendments, RECs contribute to ensuring that evolving scientific knowledge and emerging safety data are appropriately addressed.

1.4.4. Social Risks to patients involved in novel GE therapeutics

Additionally, patients may face several social risks, related to equity, access, and discrimination, by taking part in gene editing therapeutic clinical trials that extend beyond individual safety. As a result, individuals who participate in trials or are found to carry certain genetic traits related to disease may face biases in employment, insurance, or in social settings. Similarly, some individuals may be

discouraged from participating in clinical trials or undergoing testing due to fears of genetic discrimination.(59) To effectively combat these biases on a broader basis, ongoing legal efforts are needed to strengthen protections against structural discrimination and protect patients.(60) On the level of the clinical trial itself, effective education about the social risks to patients can help inform them about risks of bias and provide support in cases of discrimination. Additionally, strong data protection mechanisms (e.g. secure data storage, controlled sharing of data, involving data monitoring and safety boards) can also help protect patients' privacy as a way of preventing potential discrimination.(61)

It is also vital to note that many advanced therapies, which would include gene editing therapeutics, may be prohibitively expensive, creating a divide where only wealthy individuals or countries can benefit, while marginalized populations are left behind. In worse cases, marginalized communities may be tested on during clinical trials for a gene editing therapeutic but not have access to a treatment once it reaches market. This raises ethical questions about fairness and the right to benefit from medical innovation, underscoring the need for policies that ensure equitable access to emerging genetic technologies. Hospital exemption and compassionate use programs in the EU can serve as important pathways to addressing access and equity concerns in gene editing therapies. These pathways allow patients with serious or life-threatening conditions to receive investigational treatments outside of formal clinical trials, particularly when no alternatives exist. By enabling earlier access for individuals who might otherwise be excluded due to geography, socioeconomic status, or trial eligibility criteria, these programs can help bridge gaps in care.

RECs must ensure that patients are fully informed about the potential for genetic discrimination, particularly in areas such as employment, insurance, and social interactions, and that only certain legal protections are in place to safeguard against such biases. They must also ensure that data protection mechanisms are robust, securing participants' genetic and personal information to prevent misuse or discrimination. Although REC members do not play a direct role in determining therapeutic access once a gene editing product is commercially available, they do have responsibilities related to equity within the research context. RECs should promote fair participant selection, ensuring that marginalized populations are neither unjustly excluded from clinical trials nor disproportionately burdened by research risks. In this way, RECs contribute to distributive justice at the level of research participation, even though post-market access decisions lie outside their mandate. This includes evaluating the ethical implications of participation in trials by economically disadvantaged groups, ensuring that they are not exploited or disproportionately burdened. For instance, RECs can also recommend the integration of compassionate use programs and similar pathways that provide early access to investigational treatments for patients who may otherwise be excluded due to socioeconomic factors or geographic limitations. By addressing these ethical concerns, RECs help promote fairness, protect vulnerable populations, and ensure that the benefits of gene editing technologies are accessible to all.

1.4.5. Recommendations

Scientific & Safety Oversight:

- Ensure robust preclinical evidence supports safety and efficacy before human testing. Additionally, ensure that trials provide sufficient health care and insurance to patients during and after the trial.

Mandate long-term follow-up plans to detect delayed complications (e.g., oncogenesis, immune issues). Confirm that proposed monitoring protocols during trials are thorough and include plans for:

- Continuous clinical assessments
- Transparent reporting of adverse events
- Molecular profiling when appropriate
- Evaluate whether researchers have strategies to mitigate risks and justify potential benefits of the intervention.

Trial Design & Patient Recruitment:

- Ensure the trial adheres to all national laws and regulations (gene editing policies, patient rights, biosafety, data protection).
- Review recruitment plans for fairness and transparency, especially for rare and life-threatening conditions. Assess whether voluntariness is preserved despite emotional or psychological pressures. Ensure compensation is fair but not coercive.

Require that recruitment materials:

- Provide multiple sources of information for potential participants (Recommend inclusion of independent patient advocates or ethics consultants during recruitment).
- Use intentionally non-misleading language
- Clearly outline risks and experimental nature of intervention
- Confirm that researchers communicate post-trial care, follow-up, and access to therapy clearly.

Informed Consent:

Require clear, comprehensive consent procedures that:

- Emphasize the experimental nature and irreversible risks (the right to withdraw cannot be applied)
- Explain the difference between research and treatment
- Include alternatives to trial participation
- Promote ongoing consent rather than one-time documentation.
- Ensure that vulnerable populations (e.g., pediatric, rare disease, marginalized) are given extra safeguards.
- Confirm that information is tailored to participant comprehension levels and cultural context.
- Ensure procedures are in place to avoid undue influence by physicians or researchers.
- In pediatric trials, confirm that both parental consent and child assent are ethically handled.

Social Risks & Equity:

- Confirm that participants are informed about potential genetic discrimination in employment, insurance, or social settings.
- Require strong data protection and secure data-sharing protocols to protect participant privacy.
- Ensure equitable access to trial participation, especially for economically or geographically marginalized populations.
- Advocate for policies that support fair access to gene editing therapies post-trial (e.g., via hospital exemptions or compassionate use).
- Evaluate whether trials disproportionately burden disadvantaged communities without guaranteeing access to resulting treatments.

1.5. References and further resources

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