TAKSHASHILA INSTITUTION

Takshashila Policy Advisory

Comments on the National Guidelines for Gene Therapy Product Development and Clinical Trials

Takshashila Policy Advisory 2019-01

September 24, 2019

By Shambhavi Naik | Anirudh Kanisetti

This document can be cited as "Shambhavi Naik and Anirudh Kanisetti, *Comments on the National Guidelines for Gene Therapy Product Development and Clinical Trials,* Takshashila Policy Advisory, September, 2019-01"

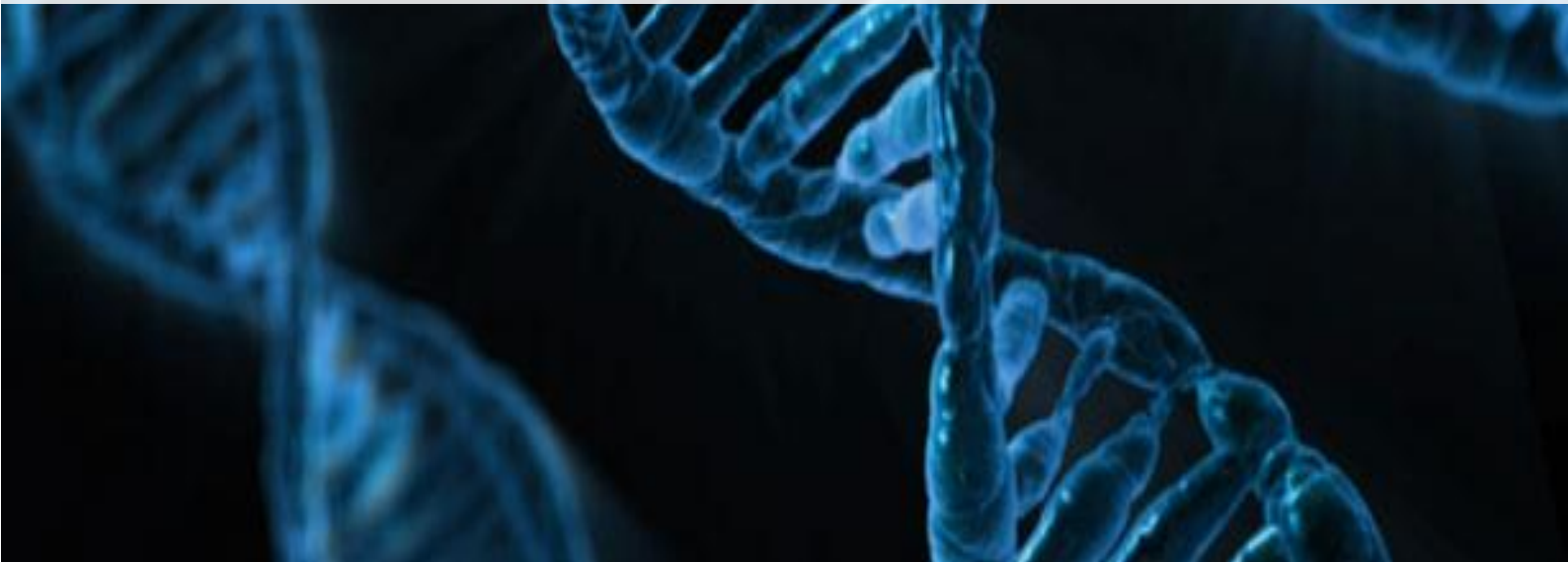

Table of Contents

Executive Summary

This policy advisory contains recommendations and comments in response to the draft National Guidelines for Gene Therapy Product Development and Clinical Trials released by the Indian Council of Medical Research (ICMR) in consultation with the Department of Biotechnology (DBT) and Central Drug Standards Control Organisation (CDSCO) in July 2019.

We note that some aspects of the guidelines require further conversation. Our comments to the guidelines focus on four distinct areas, with the following recommendations.

1. **Applicability of the Guidelines.** We recommend that the definition of "therapy" and "disease" be expressly stated. The guidelines should also clarify whether they are applicable to genetic enhancement therapies. We recommend that the guidelines not ban germline gene editing applications. Instead, they should specify standards that could be used to assess the acceptability of germline gene editing.

2. **The Guiding Principles.** We recommend a revision of the guiding principles and inclusion of the following tenets:

    a. Scientific research must not be unnecessarily inhibited by regulations.

    b. Regulation is better than outright prohibition.

    c. A technology and its applications must be viewed separately.

    d. Global and national interests must be balanced.

    e. Policymaking must be scientific and inclusive.

3. **Implementation challenges for the Guidelines.** We recommend that instead of forming another committee in addition to the existing RCGM and CDSCO to approve applications, the proposed Gene Therapy Advisory and Evaluation Committee (GTAEC) be tasked with laying out guidelines for individual diseases. In addition, we suggest that some of its functions be outsourced to independent accreditors approved by, and responsible to, the GTAEC. These accreditors can provide certificates of clearance to institutions after following the protocols laid down by the GTAEC.

4. **Capacity Building for gene editing research and translation.** We recommend that grants to laboratories include costs for raising awareness about gene editing. Further, the guidelines should also include a section on patient counselling and capacity building around services for gene editing advocacy and outreach.

Introduction

On 29th of July 2019, the DBT announced a call inviting comments on the Draft National Guidelines for Gene Therapy Product Development and Clinical Trials. This document contains our response, outlining guidelines to govern the development of gene therapies including gene editing in India.

The publication of the guidelines is a positive development as the lack of gene editing specific guidelines created an ambiguous space and discouraged investors and researchers from exploring gene therapies. The guidelines are comprehensive and provide a good starting point for a nuanced conversation around gene editing governance frameworks that India could adopt.

The Takshashila Institution has developed a framework[1] for assessing gene editing applications and setting up a governance structure. We have also had the opportunity to interact with key stakeholders including physicians, scientists and patient group representatives. These discussions have been summarised in a blue paper[2]. Our comments on the gene therapy products (GTP) guidelines are based on our own research and discussions with stakeholders.

This document focusses on these four distinct areas of the guidelines. Their status under the guidelines, our analysis, and recommendations are presented.

1. Applicability of the Guidelines
2. The Guiding Principles
3. Implementation challenges for the Guidelines
4. Capacity Building for gene editing research and translation

1. Applicability of the Guidelines

Position Under the Guidelines

In the Preamble, a gene therapy product is defined as 'any entity which includes a nucleic acid component being delivered by various means for therapeutic benefit'. Section 2 outlines the various modes through which gene therapy could be administered and extends the scope of the guidelines to DNA vaccines. Section 4 reiterates that germline gene therapy is banned in India (under the clauses of the National Guidelines for Stem Cell Research, 2017[3]).

Critical Analysis

a) Ambiguity about therapeutic benefit

There is considerable debate over the ethics of using gene therapies in humans. Research[4] has found that while many participants believe that gene editing could be used for therapeutic benefit, they agree that it should not be used for enhancement purposes. The use of gene therapies to develop enhancement therapies is widely listed as one of the risks of the technology. In the context of these guidelines then, the lack of definition of "therapeutic benefit" leaves confusion of what diseases/disorders could be included in its scope.

For example, would use of gene therapy for treating baldness be considered therapeutic or enhancement? Consequently, if treating baldness is deemed to be therapeutic, would lightening skin tones also be considered therapeutic? Conversely, there are many people who believe deafness is not a disease or disability and find the treatment for deafness offensive.[5]

In the absence of a framework to determine therapeutic benefit, there will be ambiguity as to which forms of gene therapies are acceptable and which are likely to receive resistance for approval. This ambiguity will negatively affect funding and research efforts into development of gene therapies. A clarification that all

gene editing applications would be acceptable, as long as pre-set standards are met, would incentivise funding and efforts in this area of research.

b) DNA vaccines as GTPs

The guidelines include DNA vaccines as GTPs. While DNA vaccines do fit the definition of a gene therapy product as mentioned in the guidelines, DNA vaccines do not interfere with the expression of inherent genes in the target subject. The use of CRISPR or shRNA for example, leads to changes in expression of the genes a person was born with. DNA vaccines, on the other hand, introduce a new gene sequence to synthesise proteins in human cells. These proteins then act as antigens for the body to create antibodies. Current vaccine approaches depend on the use of the antigenic protein itself. Using DNA vaccines, this protein is created inside the body. Since DNA vaccines do not necessarily interfere with the normal functioning of intrinsic DNA, their safety and efficacy standards should be different from other GTPs. Clubbing them with these forms of GTPs would unnecessarily subject them to additional regulations, delaying their development and introduction in the market.

c) Ban on germline gene editing

The guidelines reiterate the ban on germline gene editing applications in humans. Germline gene editing has remained controversial – there have been many arguments against developing such applications, but scientists in China[6] and Russia[7] have shown willingness to conduct such experiments. There are many ethical and scientific concerns associated with germline gene editing, but there are also strong potential benefits from using the technology.

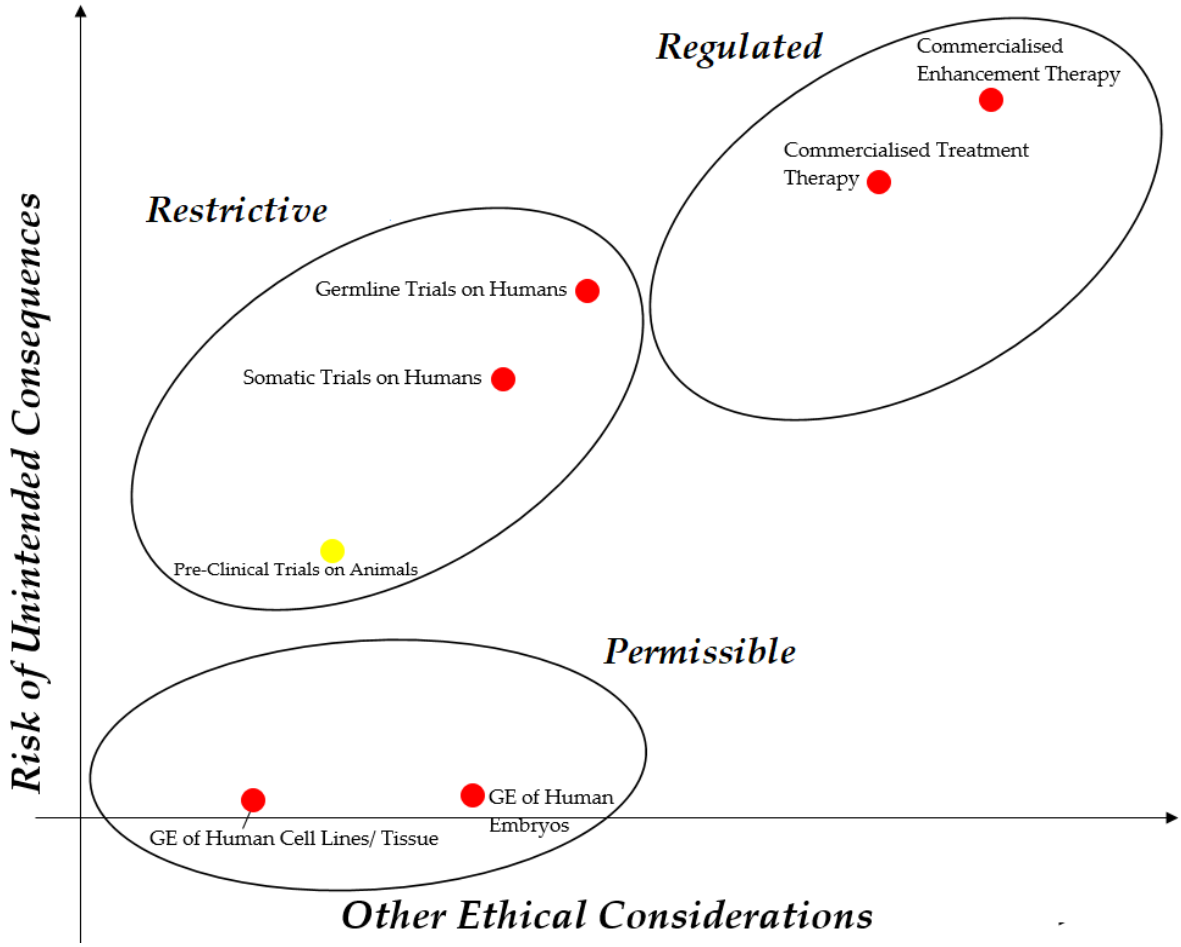

Figure 1. A proposed analytical framework for the governance of human gene editing. Not all applications require the same degree of regulatory intervention - and a blanket ban would only ensure that none of their potential benefits are explored. See Reference 1 for a detailed discussion.

Germline gene editing could be used to significantly decrease the burden of genetic disease in India. Safe germline gene editing applications would preclude the need for disease management and lower out-of-pocket healthcare expenses faced by patient families. However, the technology has not been comprehensively tested and several scientific risks still remain.

Banning the technology will not address the scientific concerns surrounding germline gene editing; those can only be solved through research. A ban on the applications will deter scientists and investors from exploring the technology, depriving many patients of potential therapies.

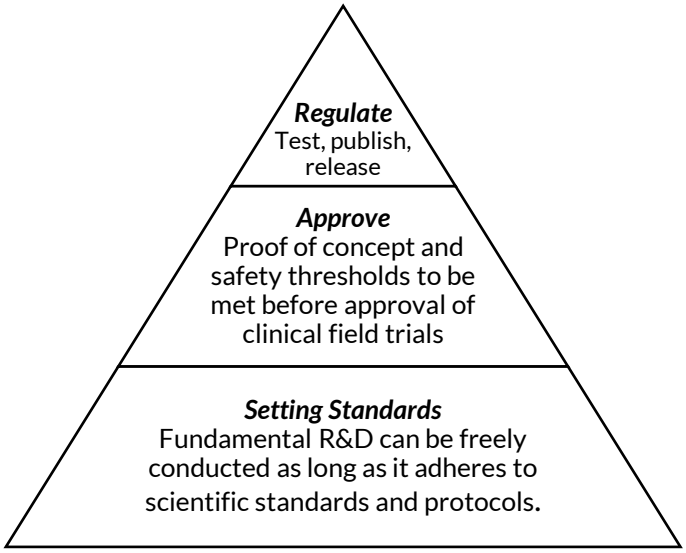

Figure 2. A proposed three-tier governance structure, with layered regulations that become more stringent as the application moves from R&D to commercialisation. For details, see Reference 1.

The WHO's Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing released a report[8] calling for the international governance of gene editing. This report does not suggest that germline gene editing should be banned, instead stating that "it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing." The Advisory Committee requests scientists keen on taking up these applications to engage with the Advisory Committee to figure out a way forward. Such an approach gives scientists the freedom to explore the technology in sync with regulatory requirements.

Overall, the scope of the guidelines will impact research and development of applications using gene editing.

Recommendations

a) Ambiguity about therapeutic benefit

A definition of which conditions these guidelines are applicable for should be included in the guidelines. Therapeutic potential can be applied to many conditions – from cancer to baldness. The ethics associated with using gene editing on these diseases are different, and therefore the guidelines cannot be universally applicable to all. We would recommend either establishing disease areas where gene therapies are acceptable, or preferably making all gene editing applications acceptable as long as established safety and efficacy standards are adhered to by the therapy developers.

b) DNA vaccines as GTPs

DNA vaccines should be left out of GTPs because DNA vaccines do not result in any change in inherent gene expression in humans and subjecting them to added

regulation might discourage creation of applications in this field. The efficacy and safety standards for DNA vaccines need to be defined separately.

c) Ban on germline gene editing

The guidelines should not ban any areas of exploratory research, such as germ line editing. Instead, the guidelines should recommend stringent pre-requisites in practices, evidence-based rationale and detailed proposals for the approval of such research.

2. The Guiding Principles

Position Under the Guidelines

The guidelines reiterate the following principles as laid down in the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017[9]:

- Principle of Essentiality
- Principles of Voluntariness
- Principle of Non-exploitation
- Principle of Social Responsibility
- Principle of Ensuring Privacy and Confidentiality
- Principle of Risk Minimisation
- Principle of Professional Competence
- Principle of Maximisation of Benefit
- Principle of Institutional Arrangements
- Principle of Transparency and Accountability
- Principle of Totality of Responsibility
- Principle of Environmental Protection.

In addition, the guidelines call for adherence to the fundamental tenets of beneficence, non-malfeasance, justice and autonomy.

Critical Analysis

While the inclusion of guiding principles is important in shaping any policy document, some of the proposed principles are contrary to the spirit of exploring new technologies such as gene editing. For example, the principle of risk minimisation indicates that care should be taken to minimise risk to the research participant. Under this principle, the situation of minimum risk is one where the participant is not subjected to a trial technology. Further clarification on how this principle should guide a researcher/physician's decisions on enrolling trial participants is required.

The first guiding principle is the principle of essentiality, which is read[10] as "The research being carried out should be essential for the advancement of knowledge that benefits patients, doctors and all others in aspects of health care and also for the ecological and environmental well-being of the planet." The ban on germline gene editing is in conflict with this principle and as such, the guidelines on germline gene editing should therefore include how it can be best used for advancement of knowledge instead of the prescribed ban. Under the principle of maximisation of benefits, enhancement therapies could also be included as an acceptable form of gene therapy.

The other guidelines are generic in nature and do not address the key challenges to shape policies for nascent, dual use technologies. The guidelines do not help in adoption of the technology and do not consider India's interest in promoting the technology.

Recommendations

Given the nascent nature of the technology and the huge benefits gene editing applications could provide in India, we recommend the inclusion of the following guiding principles:

1. **Scientific research must not be unnecessarily inhibited by regulations.** Any government interventions should aim to create an enabling environment for research but also be sufficient to mitigate these risks.

2. **Regulation is better than outright prohibition.**

   Research should be encouraged to take place in an open environment with ethical and academic oversight rather than relegate it to one without such restraints.

3. **A technology and its applications must be viewed separately.**

   Many of the issues commonly cited with gene editing and its applications, are due more to the release of the technology than anything inherent in the technology.

4. **Global and national interests must be balanced.**

   India should create a gene editing policy that serves its national interests. This approach will not only help India use gene editing to deal with its endemic problems but can also serve as a platform to take an independent stance on the global stage, as it did with generic drugs.

5. **Policymaking must be scientific and inclusive.**

   Any policy on gene editing must, first and foremost, be grounded in science. As such the policy should primarily be determined by people with the relevant scientific expertise. But given the ethical complexities and the varieties of peoples it affects, inputs must be taken from medical practitioners, patient groups and ethicists.

The guiding principles for clinical trials cannot be adequate to shape the research and development of new technologies and as such need to be revised to scrutinise their applicability to this new requirement.

3. Implementation Challenges for the Guidelines

Position Under the Guidelines

a) Formation of the GTAEC

The guidelines suggest the formation of the Gene Therapy Advisory and Evaluation Committee to evaluate and approve proposals involving gene editing. The committee is composed of the following: Chairman, Alternative Chairman, Member Secretary (ICMR), nominees from the MoHFW, CDSCO, MCI, DBT, DST, CSIR, RCGM, BIS, QCI, and biomedical experts with relevant experience in gene therapy, GTP or their applications. The biomedical experts group will be drawn from appropriate disciplines such as, but not limited to, gene therapy, haematology, pharmacology, immunology, cell and molecular biology, molecular medicine, microbiology, genetics, developmental biology, clinical medicine and nursing and may be broadened to co-opt subcommittees for specific disease areas or type of GTP administration. As per Annexure 1.2, other members include ethics

and legal experts, social scientists, lay-persons and women's representatives and subject experts as per the domain area of the proposals under evaluation.

b) Continued requirement of RCGM to pre-approve proposals before GTAEC:

Under section 6.4, the guidelines require that "GTPs should have prior approval of Review Committee on Genetic Manipulation (RCGM)."

c) Institutional Bio-safety committee requirement

Under section 6.2, "It is mandatory for all institutions and entities engaged in development of GTPs to establish an Institutional Bio-safety Committee (IBSC)."

Critical Analysis

a) Formation of the GTAEC

The guidelines suggest the formation of the apex Gene Therapy Advisory and Evaluation Committee (GTAEC) with core members and the inclusion of subject matter experts as required. This is a positive step and would help evolution of disease-specific guidelines. However, the composition of the GTAEC does not explicitly include any members from the industry. Since the commercialisation of the technology would most probably occur in industrial and not academic laboratories, representation from industry should be included in dialogue.

b) Continued requirement of RCGM to pre-approve proposals before GTAEC

Furthermore, the process flow for proposal approval is now lengthened because of the formation of this body in addition to the existing RCGM and CDSCO. The guidelines indicate that proposals involving GTPs would need approvals from RCGM and GTAEC before submission to CDSCO for further acceptance. This process will add to the time taken for approval and create barriers for entrepreneurs to work in developing GTPs.

c) Institutional Bio-safety committee requirement

Section 6.2 mandates all institutions engaged in development of GTPs establish an institutional bio-safety committee. Established academic institutions and private sector companies already have such committees set up. But start-ups and nascent companies might not have enough capacity to establish such a

committee. The requirement of a committee would also add a barrier for entrepreneurs wanting to develop GTPs.

Recommendations

a) Functioning of the GTAEC

The GTAEC should represent the end users and beneficiaries of new gene therapies. It is in India's national interest to allow the benefits of gene editing technologies to reach a wide spectrum of consumers. We suggest that the GTAEC also have representation from the biotechnology industry as well as patient groups.

The Guidelines do not leave sufficient scope for innovation and research outside of established institutions. As gene editing technologies and applications become more pervasive, the GTAEC might become a bottleneck for approvals, which will slow down the rate of scientific and economic progress. We suggest that some of its functions be outsourced to independent accreditors approved by, and responsible to, the GTAEC. These accreditors can provide certificates of clearance to institutions after following protocols laid down by the GTAEC.

b) Continued requirement of RCGM to pre-approve proposals before GTAEC

This creation of an additional committee is an added approval step which will only add time for approval. Instead a committee of mixed RCGM and GTAEC members would help expedite the process and ensure stakeholders who are associated with the particular GTP can be included in the decision-making process.

Working groups should assess projects based on genetic data, invasiveness of proposed treatment, progression of disease, mortality rates and incidence of disease. The working group should set objective thresholds of acceptable levels of toxicity and efficacy from pre-clinical and clinical trials. Particularly for toxicity, the outcome should be pegged to functional consequences (not just number of background mutations). In terms of efficacy, outcomes such as extension in life by a certain period of time may be used. A reasonable trade-off between toxicity and efficacy need to be made to approve therapies, particularly for lethal diseases. This trade-off can be made more stringent for lifestyle enhancement gene treatments.

In addition, approvals/rejections of a GTP should be time-bound in order to ensure that potentially useful applications are not needlessly delayed owing to the

large number of clearances required. A more nuanced regulatory stance is needed based on the scientific risk and ethical implications of various technologies.

c) Institutional Bio-safety committee requirement

For companies with fewer than 25 people, associating with another institution with an IBSC should be allowed.

3. Capacity Building for gene editing research and translation

Position Under the Guidelines

The guidelines refer to capacity building for providing educational support and raising awareness about GTPs. However, it does not explicitly refer to measures for executing this goal.

Critical Analysis

Gene editing is a new technology and in the absence of awareness, its adoption in the Indian market will remain poor. Further, there are already multiple ethical debates going on about the use of gene editing and can lead to confusion amongst early adopters. Hence it is critical that as policies in India support the development of GTPs, simultaneously efforts are made to educate the public on the usefulness and methods to safety explore approved GTPs.

Recommendations

a) Costs to Laboratories

Grants for laboratories performing gene editing research should contain a component for compliance costs. A defined regulation would make it easier for laboratories to get access to funds by raising confidence among potential investors.

b) Capacity Building

Advocacy and outreach are needed for lawyers and journalists involved. Counselling capacity needs to be built for patients who want to use gene editing treatment options, especially for non-therapeutic reasons. Education and training of personnel interfacing with patients would be necessary. Grants for research laboratories should include a component for public communication of their research findings.

References

[1] Madhav Chandavarkar, Anirudh Kanisetti, et al, A *Framework for Governing Gene Editing*, Takshashila Discussion Document, 2017-04.

[2] Shambhavi Naik, Madhav Chandavarkar, Anirudh Kanisetti, Ajay Patri, *Blue Paper*: A *Framework for Governing Human Gene Editing in India*, Takshashila Blue Paper, 2017.

[3] Indian Council for Medical Research and Department for Biotechnology, 2017. *National Guidelines for Stem Cell Research.* http://dbtindia.gov.in/sites/default/files/National_Guidelines_StemCellResearch-2017.pdf

[4] Pew Research Center, July 2018. "Public Views of Gene Editing for Babies Depend on How It Would Be Used". https://www.pewresearch.org/science/2018/07/26/public-views-of-gene-editing-for-babies-depend-on-how-it-would-be-used/

[5] Sharp, Gwen. "Defining Medical Problems: Is Deafness a Disease?" The Society Pages/Sociological Images. November 6, 2006. https://thesocietypages.org/socimages/2008/11/06/defining-medical-problems-is-deafness-a-disease/

[6] Rana, Preetika. "How a Chinese Scientist Broke the Rules to Create the First Gene-Edited Babies." Wall Street Journal. May 10, 2019. https://www.wsj.com/articles/how-a-chinese-scientist-broke-the-rules-to-create-the-first-gene-edited-babies-11557506697

[7] Regalado, Antonio. "A Russian scientist has threatened to make more CRISPR babies." June 11, 2019. https://www.technologyreview.com/f/613661/crispr-babies-gene-editing-scientist-china-russia-hiv/

[8] World Health Organisation, 2019. *Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing: Report of the First Meeting.* https://www.who.int/ethics/topics/human-genome-editing/GenomeEditing-FirstMeetingReport-FINAL.pdf?ua=1

[9] Indian Council for Medical Research, 2017. *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants*, 2017. New Delhi: https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf. 3.

[10] Sanmukhani J and Tripathi CB. *Ethics in Clinical Research: The Indian Perspective.* Indian Journal of Pharmaceutical Sciences 2011 Mar-Apr; 73(2): 125–130