BLUE PAPER – A FRAMEWORK FOR GOVERNING HUMAN GENE EDITING IN INDIA

This Blue Paper is the result of a Roundtable Discussion held on 15th December 2017, on the Discussion Document: A Framework for Governing Gene Editing

Takshashila Blue Paper
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ABOUT THE GOVERNANCE OF HUMAN GENE EDITING

An overview of the Discussion Document: A Governance Framework for Gene Editing in India

— The need for governance of human gene editing

— The aim and scope of the proposed guidelines

— The guiding principles for gene editing governance

— Categorisation of human gene editing applications

— The three-level framework of governance

— The implementation features of the proposed guidelines

— Key features of the proposed guidelines

Discussion Document Overview

The Discussion Document is intended to function both as a primer for gene editing as well as a proposal for the governance of gene editing in India.

Gene editing technologies have enormous potential benefits, but like other developing technologies, have limitations and risks.

The field of gene editing is advancing at a rapid pace. India needs an approach to streamline approval and monitor processes for gene editing applications so as to encourage research and innovation in a safe and responsible manner.

Takshashila's Discussion Document uses an analytical framework that categorises the various applications of gene editing on the ethical considerations and risks of unintended consequences inherent in each application. Three categories were found, which were labelled on the type and stage of research: Fundamental R&D (Laboratory), Commercial R&D (Trials), and Commercialisation (Public Release).

Based on these categories, a three-level governance framework was proposed with increasing stringency of prerequisite standards, practices and approvals determined as necessary for each category.

To facilitate research, it was suggested that independent accreditation firms be formed to audit and monitor gene editing-based projects.

Need for the Governance of Human Gene Editing

The Indian Council of Medical Research (ICMR) has issued two guidelines relevant to the field of gene editing: The National Guidelines for Biomedical and Health Research Involving Human Participants and The National Guidelines for Stem Cell Research. However, there is still no specific set of guidelines dealing with human gene editing. This should be addressed for the following reasons.

To foster research

There are a host of inheritable genetic disorders such as thalassemia and haemophilia as well as several diseases that are genetic in nature, such as cancer. A regulatory environment that is conducive to gene editing experiments is a vital part of finding treatments to these conditions.

However, this is currently not the case. There is much ambiguity in terms of which organisation to seek approvals from. Equally paradoxical are the steps required to meet obligations already specified in some of the guidelines. Increasing the clarity of regulations will thus not only improve research in India, but also enable research on endemic diseases.

To hinder quackery and malfeasance

There has already been a proliferation of illegal and dangerous activities such as IVF centres with caste biases and spurious stem cell therapies. Biohacking kits are also now available in the US; a phenomenon that is likely to repeat in India. It is necessary to try and prevent such activities from causing damage as it may turn public perception against human gene therapies.

Aim and Scope of the Proposed Guidelines

As such, we propose guidelines for gene editing research under the ambit of the ICMR that will supplement its other guidelines such as the National Guidelines for Biomedical and Health Research Involving Human Participants and The National Guidelines for Stem Cell Research.

Aim and Scope

These guidelines are intended to deal with technical issues related to gene editing of human cells or their derivatives. Many of the ethical concerns are already dealt with by the guidelines on research involving human participants. Additionally, non-human gene editing falls outside the ambit of these guidelines.

To whom shall they apply?

All stakeholders, including individual researchers, institutions, sponsors, oversight/regulatory committees or anyone else involved in the editing of human cells and their derivatives.

Focus

*1. A regulatory pathway and monitoring mechanism for basic clinical research and product development based on the **purpose of research** and **threshold of acceptability**.*

*2. Procurement of gametes, embryos and somatic/stem cells for **gene sequencing and editing**, and their **banking and distribution**.*

Guiding Principles for Gene Editing Governance

Both guidelines contain a list of general principles that should also be included in Guidelines for Human Gene Editing. However, the following principles should also be added.

Scientific research must not be unnecessarily inhibited by regulations

Any government intervention should aim to create an enabling environment for research but still mitigate any inherent risks.

Regulation is better than outright prohibition

Research should be encouraged to take place in an open environment with ethical and academic oversight. A total --and potentially unenforceable-- ban would relegate it to one without such restraints.

A technology and its applications must be viewed separately

Many of the issues commonly cited with gene editing are due more to the distribution of the technology than anything inherent in the technology itself.

Global and national interests must be balanced

India must strive to create a policy that serves its national interests while simultaneously balancing considerations from abroad.

Policymaking must be scientific and inclusive

The core details of the policy should be determined by scientists. However, given the variety of stakeholders and complexities of the topic, medical practitioners, patient groups, and ethicists should also be consulted.

Categorisation of Human Gene Editing Applications

The risks and limitations of human gene editing applications vary greatly on the type of cell being edited and the purpose of the edit. Applications were separated on these verticals and then analysed on the basis of the risk of unintended consequences and other ethical considerations. Three broad categories of gene editing were found: Permitted, Restricted and Regulated.

Bases of Categorisation

1. The Risk of Unintended Consequences

These are consequentialist considerations like impacts on health or equality that can be mitigated through laws and regulations.

2. Other Ethical Considerations

These are non-consequentialist considerations like the consent of future generations for hereditary edits. These are complex ethical issues that require value judgments to set legal boundaries.

Categories of Human Gene Editing Applications

I. Permitted

1. Genetic Editing of Human Cells/Tissue

2. Genetic Editing of Human Embryos (Pre-Implantation)

II. Restricted

1. Preclinical Trials on Animals

2. Somatic Editing Trials on Humans

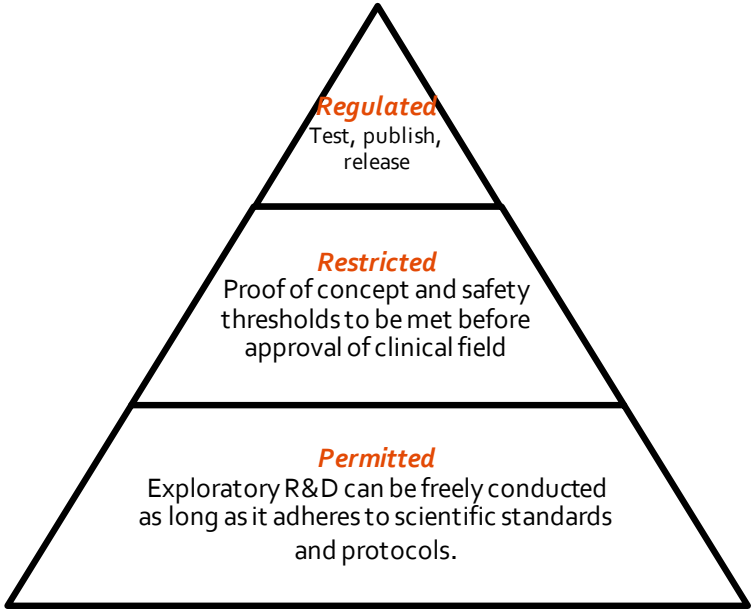
III. Regulated

1. Commercial Gene Therapy for treatment

2. Commercial Gene Therapy for Enhancement

3. Germline Editing Trials on Humans

The Three-Level Framework



Permitted Research

This category of research is to primarily gain scientific knowledge. The guidelines would apply to any organisation conducting research, irrespective of whether it is publicly or privately owned. The main concern at this stage is to follow standards and protocols. Research should be conducted in accordance with Good Laboratory Practice guidelines and the organisation should have institutional committees to maintain rigorously upheld ethical and scientific standards.

Restricted Research

This category deals with the preliminary research necessary to arrive at a final gene therapy product. Research proposals for trials should show a clear link between the gene being edited and the final product as well as how the trials meet safety and ethical standards. The final product should also meet a "threshold of acceptability" that is determined by ethical as well as scientific considerations.

Restricted Research

The primary concern with this category is damage limitation. As such, germline editing trials should pass rigorous standards and qualifications rather than be prohibited outright. Similarly, any gene therapy for public release must pass independent, time-bound and transparent tests to make sure the product is not harmful.

Implementation Features

Independent Accreditation Firms

Independent firms should be licensed to approve, monitor and audit projects based on the guidelines. These firms should themselves be subject to periodic audits to ensure compliance. This will facilitate timely approvals as there will be multiple options of a single institution to get approvals from as opposed to multiple government authorities.

Threshold of Acceptability

A major concern regarding editing of human genes is its potential to exacerbate social inequality. This cannot be solely dealt with by these guidelines as a skew in financial resources is already prevalent with healthcare in general. However, a threshold of acceptability with regard to gene editing applications, especially if they are for enhancement needs to be determined. This threshold should be objective, reasonable and be determined by a committee with the relevant expertise (both scientific and ethical).

Key Features of the Proposed Guidelines

Specific Guidelines for Human Gene Editing Applications

Given the complexity and variance between the risks associated with gene editing of plants, animals and humans, the regulatory approach for human applications needs to be different from those for plants and animals.

No Moratorium

The guidelines do not ban any areas of exploratory research, such as germline editing. Instead, the guidelines recommend stringent prerequisites, evidence-based rationales and detailed proposals for the approval of such research.

Standards are set by category of research, not the place of research

Exploratory research, whether carried in an academic laboratory or private company should adhere to similar standards. Stricter standards should apply for pre-clinical research in animals and humans. Finally, public release should have the strictest standards, regardless of whether the gene editing is being done by a private or public entity.

ROUNDTABLE DISCUSSION POINTS

The RoundTable was chaired by Prof Vijay Chandru, co-founder and Chairman, Strand Life Sciences.

List of participants at the Roundtable:

- *Dr. Alok Bhattacharya, Jawaharlal Nehru University*
- *Dr. Arkasubra Gosh, Narayana Nethrayala*
- *Dr. Gayatri Saberwal, Institute of Bioinformatics and Applied Biotechnology*
- *Dr. Namita Kumar, International Institute for Art, Culture and Democracy*
- *Dr. Ramaswamy S, Institute for Stem Cell Biology and Regenerative Medicine*
- *Mr. R S Anand, Dystrophy Annihilation Research Trust*
- *Dr. Shriram Ragavan, Evolva Biotech*
- *Dr. Sudhir Krishna, National Centre for Biological Sciences*
- *Dr. Vijay Raghavan, Department of Biotechnology & National Centre for Biological Sciences*

On the Scope of the Proposed Guidelines

Discussion Point #1: Scope of gene editing guidelines

Genetic functions can be modified through changing the sequence of DNA or changing the expression of the genes. The scope of gene editing guidelines should extend to the use of genetic material (nucleic acids) to change either sequence or expression.

Discussion Point #2: Use of gene editing for lifestyle enhancement

While therapeutic research should be prioritised, the use of the technology for lifestyle enhancement is inevitable given the economics at play. Given this, somatic editing for general disorders (not caused by genetic mutations/polymorphisms) should be allowed. This expanded scope of therapies would increase the size of the gene editing industry, thus bringing in more research that could eventually cross-subsidise the costs for life-saving therapies.

Discussion Point #3: Biobanking and the ownership of genetic data

The Justice Sri Krishna Committee is currently drafting a data protection law, while ICMR guidelines already touch on this issue. The vast resources and expertise required to maintain biobanks, as well as the complexities regarding the intellectual property of genetic data also mean that this is best dealt with separately.

On the Adaptability of Guidelines

Discussion Point #4: Enforceability

The current model of non-enforceable ICMR guidelines is sufficient to govern human gene editing in India as guidelines are more easily altered than statutory laws. The technology is progressing at a fast pace and adaptability of guidelines is preferable to enforceability.

Discussion Point #5: Revision of the Guidelines

The constitution of a Standing Committee of sorts whose role is to revise the guidelines can be considered to ensure that guidelines are kept up to date. An online system must be engineered to invite suggestions from the general public and experts.

On Protocol Standards

Discussion Point #6: Protocol Standards for Exploratory Research

Research should not be inhibited by excessively stringent standards. The current institutional safeguards are sufficient to conduct research; the requirement of conforming to Good Lab Practices (GLP) is too onerous for academic laboratories, especially small ones. However, if laboratories are expected to follow set practices, they should be clearly spelt out so that grants can then also cover the costs of compliance. Courses on ethics and counselling should also be made an integral part of institutions working with samples derived from human patients.

Discussion Point #7: Protocol Standards for Preclinical Research

Laboratories doing pre-clinical trials should follow GLP. Small laboratories (such as those funded by patient groups) which do not have institutional bio-safety/ethics committees should be allowed to leverage the capacity of a larger institution. Any change of protocols/project goals mid-way through must also be vetted by the relevant bio-safety/ethics committee that approved the original proposal; mere disclosure at a later stage may not be the safest way forward. However, this requirement can possibly be relaxed for academic research.

On Working Groups

Discussion Point #8: Working Groups

Working groups should be formed for the creation of various assessment standards of projects depending on the types of cells being edited. These groups should consist of scientists, clinicians, patient group representatives, clinical geneticists, lawyers, genetic counsellors and industry representatives. The group should have expertise/experience in the relevant research area and vested non-interests should be barred. The decisions of the working group should be made on a majority basis.

Discussion Point#9: Threshold of Acceptability

*These working groups should set their assessment guidelines based on genetic data, invasiveness of the proposed treatment, progression of the disease, mortality rates and the incidence of disease. Objective thresholds should be set for acceptable levels of toxicity and efficacy for pre-clinical and clinical trials that **focus on outcomes**. For toxicity, the threshold should be should be pegged to functional consequences rather than a number of mutations. For efficacy, outcomes such as an extension of life by a specified period of time may be used. A reasonable tradeoff between toxicity and efficacy needs to be made to approve therapies, particularly for lethal diseases. This tradeoff can be made more stringent for lifestyle enhancement gene treatments.*

On Clinical Trials

Discussion Point #10: Fast-tracking of clinical trials

There should be a procedure for fast-tracking clinical trials for gene therapies targeting rapidly lethal diseases, or patients in terminal stages of a disease. Informed consent from patients (or if they are unable to, their family members) regarding the potential outcomes and risks of the trials should be obligatory.

Another kind of trial that can be fast-tracked are those that repeat US/EU trials on Indian genotypes. These may be fast-tracked after determining the extent to which data from foreign studies can be co-opted in domestic experiments.

Discussion Point #11: Clinical trials for Rare Diseases

A clear rationale for clinical trials involving patients of rare diseases needs to be decided. Since the number of patients suffering from rare diseases is lower than other higher-incidence diseases, clinical trials involving fewer patients should be allowed. The different evidentiary requirements for such trials needs to be clearly laid down to facilitate more research on treatments for such diseases.

On Independent Accreditation Firms

Discussion Point #12: Auditing of laboratories

There is currently no mechanism to check if experiments are done according to standards (such as paper trials, dissemination, audits). The current government-run auditing capacity is inadequate. The licensing of private sector firms by the government would be a good way to expand auditory capacity without supplementing government audits. For example, for fast approvals of pre-clinical trials, a research organisation could go to the private sector at a cost, or get it for free (or a comparatively nominal fee) from the government but at a slower pace. A single regulator might not be the best option.

Discussion Point #13: Time-bound Approvals

One of the most crucial requirements of approvals is that they must be time-bound and should not be unduly delayed. The current set-up requires approaching multiple government organisations that need to coordinate with one another, leading to delays. The creation of Independent Accreditation Firms could solve this problem.

On Costs

Discussion Point #14: 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 clarity and confidence among potential investors regarding eventual outcomes.

Discussion Point #15: Cost of Therapies

If private companies are unable to patent their gene-based therapies or are subject to price controls, then laboratories would need governmental funding. This has to be a strategic decision taken by the government and taken with due consideration of the trade-offs.

On Non-Technical Capacity Building

Discussion Point #16: Awareness

Advocacy and outreach is needed for lawyers and journalists involved to make sure they understand and interact with gene editing properly. Counselling capacity needs to be built for patients who want to use gene editing treatments, especially for non-therapeutic reasons. This may be done by hiring dedicated counsellors or educating and training personnel interfacing with patients, or preferably both.

Discussion Point #17: Insurance

The government could pay for the insurance of gene editing therapies in clinical trials. The subject of genetic information should also be looked at from the perspective of insurance. The general practice right now is to consider genetic disorders as pre-existing conditions to deny coverage. This amounts to discrimination. The Insurance Regulatory and Development Authority Act and any other relevant laws need to be amended to address this.

REFERENCES

Discussion Document:

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