Final Action Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

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The Policy
Synopsis

The National Institutes of Health (NIH) Office of Science Policy issued a notice, Final Action Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, affecting how the NIH regulates recombinant or synthetic nucleic acid molecules for their use in human gene transfer clinical research. The new approach aims to reduce redundancy in reporting, as many elements of protocol approval for these products are already regulated through the Food and Drug Administration (FDA) and by Institutional Biosafety Committees (IBCs). Thus, this notice communicates that new protocols will no longer be approved by the NIH; IBCs will become the main regulatory body. The NIH instead will focus on assessing emerging technologies and on creating guidelines for IBCs to follow, but will not review specific protocols.

As the NIH will no longer approve protocols, the Genetic Modification Clinical Research Information System (GeMCRIS) will no longer be used. It has not been updated since August 2018, and will no longer be accessible after September 30, 2019.

Importantly, the notice also changes the role of the Recombinant DNA Advisory Committee (RAC), which in the past oversaw the review of specific protocols submitted by researchers on research involving recombinant or synthetic nucleic acid molecules. The NIH has renamed the committee as the Novel and Exceptional Technology and Research Advisory Committee (NexTRAC). NexTRAC’s goal is now to provide recommendations on regulation standards by assessing emerging technologies, rather than assessing individual protocols. NexTRAC's first meeting is anticipated to be held in late 2019.

Context

In 2017, the first three gene therapies were approved by the FDA. Given this recent trend of gene therapies integrating into clinical treatment, the NIH and the FDA have moved toward a streamlined oversight process pertaining to gene therapy trials. The NIH Director, Dr. Francis Collins, and the former FDA Commissioner, Dr. Scott Gottlieb, wrote that “there is no longer sufficient evidence to claim that the risks of gene therapy are entirely unique or unpredictable – or that the field requires special oversight that falls outside our existing framework for ensuring safety.”

According to Collins and Gottlieb, the impetus behind the modification of the guidelines was to bring human gene therapy clinical research in line with the same regulatory framework involved in other clinical research. This means denoting IBCs as the main regulatory body for gene therapy trials such as is done for other types of clinical trials; protocol registration submission and reporting will no longer be handled by the NIH. IBCs are review bodies found within research-conducting institutions (i.e. the National Institute of Environmental Health Sciences has its own IBC, as does Boston University, etc.) IBCs are tasked with making sure that specific protocols comply with NIH regulations and recommendations, as well as considering their particular community’s priorities. This means that acceptable safety standards within IBCs vary, but they should never be lower than the standards set by NIH regulation. The NIH mandates that IBCs have at least five members, with at least two of them not affiliated to the IBCs institution, and at least one plant specialist and one animal containment expert.

The RAC was established in 1974 with the goal of providing recommendations to the NIH Director on issues of science, safety, and ethics surrounding recombinant DNA trials, and in 1990 began oversight over human gene therapy trials. From 1982 to 1991, there also existed a Human Gene Therapy Subcommittee that oversaw the creation of the document that set out the guidelines for research, as well as reviewing individual protocols. Because of the redundancy between it and the
The Debate

The Science

Science Synopsis

DNA [29] is a molecule that holds the biological instructions necessary for building our bodies. DNA is made up of strings of nucleic acids [30], which can be grouped into genes [31] – one could think of this as though it were a book, with nucleic acids as the letters in the book and genes as the chapters. Nucleic acids can also be found in RNA [32], which play an important role in ensuring that the appropriate “instructions” are expressed at the correct locations at the right times.

There are small differences in DNA sequences from person to person. While most of these differences are not thought to relate to health concerns, and instead are linked to traits differences such as hair color or height, some diseases are impacted by variations in an individual’s DNA, known as mutations. For example, some forms of cancer [33] and of vision loss [34] are associated with mutations in single genes.

Gene therapy [35] refers to a clinical treatment that aims to treat or prevent diseases that are caused by mutations in the DNA sequence. This is accomplished by delivering nucleic acids (either DNA or RNA) to the patient, with the goal of either replacing the gene in the patient’s body that has a known mutation, inactivating the gene with the mutation, or for providing a new gene to fight the disease.

There are different methods of both creating the nucleic acids used for gene therapy, and delivering these genes into the patient. Of note is that, in the US, gene therapy is only available to patients after they are born; conducting gene therapy on fetuses is currently prohibited [36]. Specifically, this NIH notice alters the method of regulating the nucleic acids that are delivered to patients undergoing gene therapy, including:

- Recombinant nucleic acid molecules [37], which are created by swapping out small portions of an already existing gene (i.e. recombining) to obtain the desired form;
- Synthetic nucleic acid molecules [38], which are made by artificially and sequentially stringing the appropriate nucleic acids; and
- Cells [39], which contain recombinant or synthetic nucleic acid molecules, which are used in the delivery of these nucleic acids to individuals receiving gene therapy.

Scientific Assumptions

- **Gene therapy is an effective way to cure or prevent certain diseases** There are many studies on the efficiency of various gene therapy treatments. Research indicates that it is a relatively effective treatment for some diseases, although some researchers propose alternative methods may at times be better suited, especially for older patients.
- **We understand the risks posed by gene therapy, and those risks are similar to those posed by other clinical trials** Researchers have extensively investigated gene therapy and they agree that, while we understand a great deal about this procedure and possibly comprehend most of the risks, there remain uncertainties around the risks posed with gene therapies. Of special note is the uncertainty surrounding downstream effects of gene therapies delivered through viruses.
- **Gene therapy can have a long-term effect on patients through the incorporation of inserted nucleic acids into the patient’s own DNA** Studies have tracked the long-term effects of gene therapy confirm that the effects persist for many years, although no studies have directly confirmed that this is due to incorporation of inserted DNA into the patient’s own DNA. Some studies that used viruses as the delivery mechanism have reported adverse effects developing many years after treatment, presumably from the inserted DNA moving into off-target cells in the patient.

The Debate

Scientific Controversies / Uncertainties

The primary uncertainty regarding the updated NIH guidelines is whether our understanding of gene therapies is sufficiently robust [40] such that standard clinical trial regulatory process is enough to ensure the safety of patients. There have been several cases of adverse effects reported in clinical trials. Gene therapies delivered via viruses seem particularly prone to leading to adverse effects [41] and these protocols remain the least understood [44]. However, many studies also indicate that gene therapy treatments are safe [45] and effective [46] for patients with a variety of conditions. Researchers state that carefully designing [41] treatments should be able to curb most of the potential adverse outcomes. Additionally, some researchers [47] argue that, despite the risks, study and development of gene therapies is important for furthering our ability to treat diseases for which we currently have no other cures.

It is worth noting that many studies are limited to a relatively small number of patients. This means that, even with the large study sizes required for Phase 4 [49] of the FDA drug approval process, it is possible that researchers will not see adverse effects in their clinical trials that might emerge when the therapy is taken to market. This is due to frequent biases [50] in the target patients of trials; adverse effects could emerge as the treatment reaches additional individuals [51] who may have metabolic variations, other medical conditions, and differences in lifestyle that were previously unaccounted for.
Endorsements & Opposition

- Mildred Cho (Bioethicist at Stanford University and Member of the RAC), statement, August 15, 2018: “This is not the right time to be making any moves on the idea that we know what the risks are.”
- Marcy Darnovsky (Executive Director of the Center for Genetics and Society), statement, August 15, 2018: “We need to strengthen rather than weaken the review apparatus if the FDA were to start to consider proposals.”
- Jeffrey Kahn (Director of the Johns Hopkins Berman Institute of Bioethics), statement, August 15, 2018: “We have mechanisms in place to protect patients. It doesn’t need to be treated as a special case in clinical research any longer.”
- Leigh Turner (Associate Professor at the University of Minnesota), statement, August 15, 2018: “This is something the FDA has the tools to handle. I don’t think this is somehow a massive deregulation.”

Potential Impacts

- Francis Collins (Director of the NIH), statement, April 25, 2019: “NIH is refocusing the NIH Recombinant DNA Advisory Committee (RAC) into a role closer to its original mandate, which was to follow and provide advice on safety and ethical issues associated with emerging biotechnologies. Today, these emerging areas of research include, but are not restricted to, technologies surrounding advances in recombinant or synthetic nucleic acid research.”
- Carl Elliot (Bioethicist at the University of Minnesota Center for Bioethics), article, May 26, 2015, writing about Intuitional Review Boards (IRBs), which are very similar in nature to IBCs: “With so much money at stake in drug research, research subjects need a full-blown regulatory system. IRBs should be replaced with oversight bodies that are fully independent—both financially and institutionally—of the research they are overseeing. (…) And they must have the power to punish researchers who break the rules and institutions that cover up wrongdoing.”

Status

This decision was issued by the NIH on April 26, 2019.

Recommended Citation


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