ALLIANCE for Regenerative Medicine

The Recombinant DNA Advisory Committee (RAC): Future Roles

This document was written by the Regulatory Committee of the Alliance for Regenerative Medicine (ARM) in conjunction with ARM's Gene Therapy and Gene-modified Cell Therapy Section.

RAC oversight no longer needed for "non-novel" gene therapy approaches

Gene therapy research and clinical development have become more prevalent in the last 40 years and the understanding of the complex scientific, ethical, and legal issues related to recombinant DNA technology have grown as well. The RAC was initially created because of the novelty of gene transfer and concerns about public acceptance and understanding of the technology. These concerns have lessened as gene therapy technologies have become more widespread and accepted. There are currently 207 open gene transfer trials listed on clinicaltrials.gov, mostly using technologies that are "non-novel" (e.g. LVV, gamma retro, AAVs, non-viral plasmid). The risks surrounding these approaches are better understood. Extensive scientific knowledge has been accumulated in the past 15 years and long-term clinical data is now available for these approaches.

It is still appropriate to discuss bioethics issues for clinical trials; however, this can be achieved within clinical trial review bodies currently established at clinical sites. Most clinical centers now have appropriate expertise to provide sufficient oversight on clinical trials involving existing gene therapy technologies. Most centers either have 1) created an Institutional Biosafety Committee (IBC) at the clinical site staffed with physicians and/or researchers with expertise in gene therapy that can appropriately evaluate the risk benefit to subjects in any given gene therapy clinical protocol, 2) outsourced the IBC function to a central IBC to perform the same function, or 3) in some cases, the Institutional Review Board (IRB) has physicians and researchers with sufficient training and expertise in gene therapy so that gene therapy clinical protocols can be appropriately evaluated by the IRB. ARM includes several companies that are developing non-viral or viral gene therapies and are currently running mid-stage (Phase II) clinical studies at more than 20 clinical sites in the United States. In their collective experience, US clinical sites have incorporated thorough review processes to ensure appropriate oversight of gene therapies. Often, oversight includes scientific review, IBC and IRB reviews. RAC review is now duplicative in most situations (Koehler et al, 2013).

The RAC's role to provide oversight at a national level for non-novel gene therapy products is redundant with the FDA's oversight of Gene and Cell Therapy products. FDA/CBER/OCTGT[1] has strong knowledge of gene therapy products, many years of experience with the science of gene transfer, and provides thorough review of all INDs[2]. Since 1997, FDA has issued 20 guidance documents on the development of cell and gene-based therapies, including 10 specific to gene therapies: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Cel

[1] CBER: Center for Biologics Evaluation and Research ; OCTGT: Office of Cellular, Tissue and Gene Therapy
[2] IND: Investigational New Drug Application

lularandGeneTherapy/default.htm. Additional supportive review from the RAC is not needed for protocols involving "non-novel" gene therapy approaches.

In addition, the requirement to undergo reviews from both RAC and FDA is a lengthy process for sponsors to undertake prior to initiation of a clinical trial and the RAC review process creates an additional burden. The need to undergo multiple reviews by the RAC and FDA may delay the start of new clinical trials as questions from each agency are addressed separately.

The input from the RAC for "non-novel" gene therapy approaches offers limited added value as many of the ethical and scientific issues with these types of technology have been discussed previously in the context of prior research. An example is the use of the same vector for a different but similar clinical indication is proposed. After a sponsor submits a full application, the RAC will itself declare that a full public review is not necessary. Thus, the oversight role of the RAC on gene therapy products needs to be re-evaluated, clarified and re-focused.

RAC should focus on novel gene therapy approaches

ARM views the scientific review from the RAC valuable for protocols using novel technologies -- particularly technologies incorporating approaches not previously used in humans. For example, when a proposal to use an *in vivo* epigenetic re-patterning technology in humans will be put forward, having an additional review by the RAC prior to FDA and IBCs/IRBs reviews would be beneficial. Thus, RAC review should only be required for protocols using novel technologies.

A tiered, risk-based approach could be used to determine whether a technology should be considered novel and whether a RAC review may be necessary. For example, a sponsor could submit a proposal describing the planned research, including a brief description of the technology and a clinical protocol synopsis. RAC could then decide whether further review is needed. If it determines a review of the product is needed based on the product's novelty or risk level, the review could be initiated. If a review is determined not to be needed, the RAC process would stop and no additional submissions would be required by the sponsor. We suggest that the review of the RAC be focused primarily on first-in-human studies using a novel technology or a novel vector. If this approach is pursued, greater clarification will be needed regarding the requirements for submissions for each step of the process.

The RAC review process should be improved

Even if the RAC review process focuses on emerging technologies, we believe it needs to be improved. The amount and organization of information required by Appendix M of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) should be reevaluated and streamlined. Many sections of the Appendix seem redundant and it is not clear what information is of most value to the RAC.

The RAC should consider revising Appendix M and also allowing sponsors to submit information in the format that will ultimately be filed in the corresponding IND for their review, such as Investigator's Brochure, Module 2.5 or Module 3 sections in Common Technical Document (CTD) format or Sections 7

and 8 of the usual US IND format, in place of Appendix M. Allowing sponsors the option to utilize documents they will author for other required regulatory submissions would further reduce administrative burden while still providing the scientific information requested by the RAC.

Additionally, as more and more biotechnology companies develop gene therapy products, the RAC process should be equipped to deal with trade-secret and confidentiality issues of concern to industry sponsors. The NIH guidelines do not currently exempt privately funded research from the RAC review process in the case where institutions conducting the privately funded study may receive NIH funding for any recombinant DNA research. The RAC public forum was designed as a transparent exchange of ideas related to research with recombinant DNA technologies; however, the public nature of most information provided in writing poses a challenge particularly for sponsors with commercial interests as there is concern regarding protection of proprietary information and development strategies. The public forum for RAC discussions and inability to ultimately control what the RAC determines to be public versus confidential information is an important point of consideration for sponsors in the submission of information to the RAC, particularly since documents can be made available through the Freedom of Information Act for investigational products. The amount of information available in the public domain for gene therapy products is far greater than what is normally available in the early stages of development of conventional drugs, including biologics.

In the spirit of transparency, the relationship between the RAC and FDA could also be clarified. This would enable sponsors to better plan for reviews from both agencies as the goals and contributions of each would be better understood. FDA has the authority to enforce recommendations or modifications made to a clinical study protocol. The purview of RAC is to provide a public forum to discuss scientific issues in the field of gene therapy. The potential impact of a negative review by the RAC and the related implications for Sponsors are not clear.

Reporting requirements and notification of new investigators should no longer be required

Following initial RAC review, the reporting processes for gene therapy clinical protocols requires sponsors to:

- Notify the RAC of study initiation at each participating clinical site;
- Submit information on new investigators and institutions involved in the trial;
- Submit annual reports on the study; and
- Submit safety reports.

RAC reporting requirements for new clinical sites, safety reporting, and annual reports, are redundant with those sponsors also provide to FDA and IRBs. Streamlined reporting processes across the multiple reviewing bodies would be helpful. Relief of some of the reporting requirements could allow those resources to focus on forward-looking regulatory strategies for the therapies in development.

Additionally, we recommend streamlining and focusing the use of the NIH/FDA Genetic Modification Clinical Research Information System (GeMCRIS) for gene therapy products. Minimal information could continue to be provided on the gene therapy product in the spirit of scientific exchange, but since

posting to clinicaltrials.gov is also required for most clinical trials, we believe details of the studies and protocols are better suited to this latter forum.

The RAC should continue its role to bring experts together to discuss broad gene therapy issues

The RAC should continue to bring experts together to discuss particular issues relevant to gene therapy and expand its focus on emerging technologies. This role in facilitating ethical and scientific exchange and consensus building on forward looking issues would be of added value to the scientific community and could serve as additional context and reference for regulatory review bodies such as FDA or IRBs/IBCs. This role is consistent with the RAC's charter and history and could help in the drafting of regulatory guidance documents.

Conclusion

Historically, the RAC has served an important function. We encourage evolution of the regulatory process for evaluation of gene therapy clinical trials and envision a streamlined role for the RAC. We recommend creating a new risk-based approach to determine whether RAC review is needed. We encourage the RAC to focus its reviews on truly novel gene therapy technologies and expand its role in publicly discussing broad scientific and ethical issues related to emerging novel gene therapy technologies.

Reference

Koehler et al, 2013 – Editors: Rebecca N. Koehler, Bruce M. Altevogt, Lawrence O. Gostin – Title: Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee – Report Published by the Institute of Medicine of the National Academies. The National Academies Press – Washington, D.C. – www.nap.edu