

Protection at the cutting edge: the case for central review of human gene transfer research

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Favourable results from recent clinical trials of human gene transfer (HGT) suggest that gene therapy (defined as the therapeutic or experimental administration of genetic material to human beings) may finally be recovering its repute and promise. Yet, even in success, HGT has suffered a series of setbacks, most recently with the onset of a rare leukemia in 2 children who underwent successful treatment for adenosine deaminase-severe combined immunodeficiency.^{1,2} Such unexpected complications, together with the increasing volume of novel biomedical research, invite discussion of whether cutting-edge biotechnologies like HGT merit special safety and ethics review.

The question has particular relevance in Canada, which ranks 4th worldwide in HGT trial volume,³ with approximately 40 trials completed or under way (Dr. Anthony Ridgway, Biologics and Genetic Therapies Directorate, Health Canada: personal communication, May 5, 2002). A decade after 2 reports recommended otherwise,^{4,5} Canada remains without an HGT central review body;⁶ it has, however, considered establishing central review for stem cell research⁷ and for xenotransplantation.⁸

The most prominent function of central review is in assuring trial safety and quality. HGT agents are designed on principles different from those for classic pharmaceuticals: whereas the latter are inanimate and derive their biologic activity from their molecular structure, HGT agents are potentially transmissible and function on the basis of genetic information. Because medicine has little precedent for using genes and viruses as therapeutic modalities, the properties of HGT technologies are often difficult to anticipate. Among the obstacles to designing safe trials are the weakness of animal models for estimating maximally tolerated doses in humans,⁹ the frequency of threshold toxic effects,¹⁰ the hazards of viral recombination and accidental gene transfer to hospital personnel, the poorly characterized risks of insertional mutagenesis (in which a hazardous mutation is caused by the introduction of foreign DNA sequences into the genome of the HGT recipient) and the possibility of inadvertently affecting the germline of trial participants. Central review manages these risks by pooling expertise to minimize uncertainties and vet trial quality and safety.¹¹ Additionally, the US HGT review body, the Recombinant DNA Advisory Committee, organizes safety conferences and publicly maintains databases and adverse event reports, thus enabling investigators to design safer trials.¹² In contrast, drug safety agencies and research ethics boards (REBs) generally protect the confidentiality of any information they receive.

In the context of clinical trials, many scientific questions are embedded in issues of research ethics: How should risks and benefits be weighed? When is the appropriate time to begin trials of a novel agent? Should such trials be conducted in relatively healthy volunteers, whose consent is less likely to succumb to the coercive pressures of their illness?¹⁰ Though REBs routinely grapple with such questions, their lack of expertise strains their capacity to evaluate HGT experiments. Moreover, because central committees enjoy a panoramic view of HGT, they are in a better position than REBs to render uniform judgements across similar trials.⁵ Central review also safeguards against 3 other issues that particularly imperil HGT trial ethics: financial conflicts of interest,¹³ unrealistic expectations of clinicians and participant-subjects¹⁴ and use of vulnerable research subjects (HGT trials disproportionately target children and the terminally ill).

Countries such as the United States also use central review to evaluate social concerns surrounding HGT.¹⁵⁻¹⁷ Interventions such as in utero and germline gene transfer would extend the frontiers of medicine into an intergenerational realm, and genetic enhancement expands medical practice further into healthy populations. Each practice raises concerns about harms that are collective and prospective rather than individual and immediate. For instance, do germline and enhancement therapies endanger equality and respect for diversity, and do genetic enhancements undermine social values, as when the use of anabolic steroids in athletics erodes our valuation of discipline?¹⁸ Such questions are too broad for the review mandates of REBs and drug safety agencies.¹⁹

A final function of central review is engaging the public, which remains hopeful but concerned about HGT applications.^{5,20,21} By disseminating information, central review bodies enable the public to participate intelligently in HGT policy discussions. Central review also provide a forum in which conflicting safety, ethical and social claims can be aired, challenged and resolved.²² Finally, when review bodies meet publicly and allow public participation, they nurture trust and encourage aggrieved parties to recognize the legitimacy of unfavourable decisions.²³

According to some critics, central review duplicates quality-control measures that are built into the clinical research process and therefore delays the delivery of potentially life-saving technology to terminally ill patients.²⁴⁻²⁶ Some sceptics have also argued that central review lacks a logical basis, since HGT does not present any issues not already rehearsed by conventional therapies.²⁷

However, some redundancy may be desirable in so new and dynamic a field.²⁸ Other concerns about redundancy can be addressed by focusing review only on “novel” trials.²⁹ Furthermore, the argument that central review impedes research is contradicted by one of the most authoritative reviews of the subject³⁰ and the fact that the largest volumes of HGT experiments are in countries with central review. Finally, the claim that central review obstructs access to lifesaving interventions derives from excessive optimism and a misunderstanding of the research process, which is directed at generating knowledge rather than delivering treatment.^{18,31}

Although critics are correct to charge that few of these issues are unique to HGT, uniqueness is not the only criterion for establishing additional oversight. HGT raises many concerns concurrently or with higher frequency than conventional drug research. Central review is therefore grounded in the logic that review stringency should be commensurate with the number and magnitude of an endeavour’s medical, ethical and social hazards. In addition, many of HGT’s nonunique social and ethical questions remain unsettled. By “illuminating . . . questions about research design and ethics that are not clearly or systematically showcased in any other forum,”³¹ central review produces generalizable insights into research ethics. Finally, central review compensates somewhat for the deficiencies of an overburdened system for protecting human subjects.

The Canadian government has stated its preferences for resolving biotechnologic safety and ethical questions with federal advisory bodies,^{32,33} public consultation and openness,^{32,33} and science-based risk assessment.³² Central review promotes each. Although some may find central review a nuisance, many scientists, ethicists and policy-makers concur that HGT has only been enriched by the scientific exchange, ethical practice and public discussion that central review has engendered.

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