



Perceived Benefits of Participation in Gene Transfer Research

gene transfer research is one of the most rapidly growing fields in biomedical research today, with more than 400 (mainly early phase) studies underway in the United States since 1990. To date, 67% of all clinical gene transfer research is oncology research; only 14% of studies focus on single-gene disorders, like cystic fibrosis or hemophilia, which were the original targets of this research. These studies employ unique technologies and have a unique history and public image; yet, they are also emblematic of many areas of clinical research. ▶

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▶ Despite their early-phase status with only small numbers of study subjects, gene transfer trials that aim to correct the genetic defects responsible for hemophilia have generated a great deal of interest, enthusiasm and hope. They are seen by many as “cutting-edge technology” that holds great promise for the future, and many study volunteers are motivated by the desire to contribute to that future promise in any way they can. Yet, as with other kinds of early-phase research, it is also not uncommon for patient-subjects and physician-investigators to be motivated by the hope that subjects in these first gene transfer trials will, themselves, benefit from the research intervention. In this regard, the question of what subjects might expect for themselves, and what investigators might expect for subjects from participation in early-phase research becomes a topic of concern for all interested in protecting research subjects and providing them with the information needed for an informed and voluntary decision about research participation.

Hope may be a reasonable motivation when it comes to participation in early-phase gene transfer trials, even when there is little or unknown chance of success. Yet, how can a potential subject evaluate the chances? How do clinical researchers and patient-subjects discuss and understand the prospect of benefit from gene transfer



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research, when efforts are still in the early stages? This is the subject of the research the authors and colleagues at University of North Carolina and National Institutes of Health,¹ have been conducting for the past three years.

Funded in 1999 by the Ethical, Legal, and Social Issues (ELSI) Program of the Human Genome Institute, we have undertaken three data collection activities to address this issue. First, we have analyzed nearly all gene transfer research consent forms and protocol documents submitted to the Recombinant DNA Advisory Committee since 1990 (about 350), looking at how they describe potential benefit to subjects. Second, we have conducted telephone interviews with investigators, study coordinators and research subjects in about 40 early-phase gene transfer research stud-

ies with adult subjects initiated during 1999 and 2000. These interviews include questions about how subjects made the decision to enroll in a clinical gene transfer trial and their reasons for participation; how the possibility of benefit to subjects is understood and how it is described; general views about research and research relationships; and information about the roles of the principal investigator and study coordinator in the trial. Finally, we conducted telephone interviews with representa-

tives of institutional review boards (IRBs) at institutions that have sponsored gene transfer trials during this same time period, focusing on how they approach the discussion of benefit in gene transfer research and other clinical trials. Our ultimate goal is to compare and contrast views about the possibilities of benefit to subjects held by all relevant parties in order to shed light on a much-neglected topic.

People decide to participate in clinical trials for many different reasons and perceive a number of different types of possible benefits—from improved health for themselves, to the psychological satisfaction of “doing something” about their problem, to helping patients like themselves in the future and contributing to the advancement of knowledge. In our study, we are examining three distinct types of benefit: *direct benefit* (benefit to subjects from receiving the intervention being studied); *collateral benefit* (benefit anticipated for all subjects by virtue of being a subject in a study, rather than by virtue of receiving the intervention being studied [for example, the provision of free care or the assertion that “patients get better treatment on study” because of increased monitoring, state-of-the-art testing, etc]); and *benefit to society* (to scientific knowledge or to future patients, rather than to current subjects). In addition, we are examining three dimensions of benefit *to subjects*, which sometimes overlap: the nature, magnitude and likelihood of any potential benefit, either direct or collateral.

Until now, researchers and the institutions charged with overseeing their research have focused almost entirely on making sure that subjects understand the nature, magnitude and likelihood of risks of harm that may result from participation. The possibilities of direct benefit to subjects have often been described vaguely, with such enigmatic phrases as “personal benefit cannot be guaranteed” or “you may or may not benefit.” In preliminary analysis of our inter-

views with IRB representatives, we found a surprising level of divergence about fundamental questions, such as whether potential benefit to subjects or benefit to society should be of foremost importance in a clinical trial; whether collateral benefits should be mentioned in the consent form or deleted because they might represent an undue inducement; and whether statements about potential direct benefit should be kept vague or be made more specific. While we are just beginning to analyze interview data from the 40 gene transfer trials, we have also found a great deal of diversity in whether or how people talk about the nature and likelihood of benefit, reinforcing our notion that a common language to discuss benefit does not yet exist.

Similarly, in our assessments of consent forms and protocol information, we have found divergent philosophies about disclosing benefit information. Many consent forms provide considerable information about potential benefit to subjects early in the document, in introductory sections describing the background of the study and its purpose. In contrast, the consent form sections devoted to potential benefit are often quite short, and limited to the vague statements noted above – raising the possibility that differences in information in different parts of the consent form could cause confusion. Only a small minority of consent forms attempt to


explain whether the achievement of a “surrogate endpoint” (laboratory measurement) is likely to have a clinical impact that subjects may feel. Thus, a consent form for a hemophilia study might mention the possibility of an increase in the percentage of circulating factor in the blood without necessarily discussing how great an increase would be required to reduce the number or severity of bleeds or the need for on-demand factor infusions. Even fewer consent forms describe how likely any clinical impact may be, or how long it might last if it were to occur.

And even though the majority of gene transfer trials are phase I studies, most consent forms use at least some terminology that reinforces the perception that subjects

will benefit. This includes referring to subjects almost exclusively as patients, and referring to the experimental gene transfer intervention as “treatment.” In most consent forms, the same intervention is sometimes called treatment, other times labeled with a mixed term like “experimental treatment,” and still other times labeled with a purely research term like “study intervention,” a neutral term like “infusion,” or an acronym devised for the study, like “AdF8 gene.” Again, seeing this amount of both vagueness and variety within consent forms raises the possibility that confusion for subjects could result.

Genetic research

is revolutionizing our understanding of disease and medical treatment, and confidence in genetic explanations and technologies has deeply affected both public and scientific discussion about it. The tendency to overestimate the possibility of direct benefit to subjects may be especially strong in gene transfer research.¹ Even gene transfer research’s common name, “gene therapy,” contains the implication of successful treatment. Yet its highly technical nature also raises questions about the ability of subjects, the public and even IRBs and the biomedical community to define, discuss and evaluate its benefits and risks. Overestimation of the chance of direct medical benefit, when it results from misunderstanding or lack of thorough discussion, could undermine informed consent. If clarification is needed, it is needed not only for the benefit of patient-subjects, but also for investigators, study coordinators, referring physicians, IRB members, policymakers, the press, the public and patient advocacy organizations.

Through research, it is hoped that clinicians will be able to speak to this important emerging field and also to make observations and draw conclusions of interest to clinical research more broadly. We believe that presentation and discussion of direct and collateral benefit can and should be improved in the consent process. We expect that the results of our study will not only identify challenges to informed consent, but also highlight successful approaches to the discussion of benefit to subjects. And finally, we want to lay the groundwork for thinking through, and even debating, the meaning and implications of the this kind of examination of views about the consent form and process in clinical gene transfer research. 

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