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Protecting Research Subject Welfare in Preventive Trials for Autosomal Dominant Alzheimer's Disease

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Case Introduction

With advances in medical science come new challenges in protecting the welfare of human subjects. Our ability to identify individuals at risk of catastrophic illness may lead us to new understandings of subject vulnerability. How ought we identify and recruit genetically unique research subject populations from which much can be learned but direct benefits are absent? What level of understanding ought we require of these subjects and how must we assess their understanding? The case we present here along with three accompanying commentaries address these issues in the context of early phase preventive trials for Alzheimer's disease.

Accompanying the case summary are commentaries by Mark Yarborough, PhD, University of California Davis, who discusses how highly targeted recruitment from a narrowly defined population places a "high price of admission" in terms of the burden on potential research subjects. Stanley Korenman, MD, and John M. Ringman, MD, of UCLA Medical Center, along with Stuart Finder, PhD, of Cedars-Sinai Medical Center, focus on the ways in which the eligible patient population may be vulnerable and recommend measures to best protect their welfare. Then Anne Simpson, MD, CMD, from the University of New Mexico Health Science Center Institute for Ethics, explores barriers and facilitators to potential subjects' understanding of research.

Case Summary

Investigators requested an ethics consult about a proposed study for a vaccine to prevent a monogenetic version of Alzheimer's disease. Ongoing research with two large family cohorts identified an autosomal dominant, fully penetrant gene. Symptom onset is between

35 and 50 years of age. Many family members live in a rural area of Mexico, while others have migrated to Mexico City and the United States. Members of these families are aware, to varying degrees, of their susceptibility to early onset dementia. The educational level, degree of acculturation, English language proficiency, medical sophistication, and attitudes toward research participation vary greatly among family members.

Subjects enrolled in the cohort studies travel to the U.S to undergo imaging, as well as neuropsychological, behavioral, and biochemical testing. Genetic testing results are not returned as part of the research protocol per se, but if subjects want to know their genetic status, the investigators facilitate their meeting with a genetic counselor and subjects can undergo testing outside the study, at no cost to them.

The study team's proposed plan is to conduct a randomized, placebo-controlled trial of an experimental Alzheimer's prevention agent (a β -amyloid antibody). The goal of the trial is to prevent or delay cognitive decline. All eligible asymptomatic family members will be recruited to participate in the trial. All subjects enrolled in the intervention study would undergo genetic testing on a research basis. Subjects found to carry the mutated gene would be randomized such that two-thirds would receive active treatment and one-third would receive placebo for the duration of the study. Subjects found to not carry the mutated gene undergo all study procedures but receive placebo. Although subjects will not be explicitly told their mutation status, persons having—or believed to be having—side effects from the intervention might infer (rightly or wrongly) that they carry the mutated genes. Similarly, the genetic status of all study subjects might be inferred by others in the communities.

This is an investigational vaccine that has not been used in humans before. The study team expects some subjects to experience serious adverse events, although the exact nature and likelihood are impossible to predict. Subjects who do not have the mutated gene undergo the risks of participation (including study interventions and the inference of genetic status) without any prospect of personal benefit.

The investigators were seeking advice about how to provide appropriate protections to a cohort with varied levels of education, acculturation, medical sophistication, and knowledge and attitudes toward research participation. This study raises questions about risks, results disclosure, and consent. How would you recommend these and other ethical issues be addressed for this study?