Ethical Issues in Alzheimer’s Disease Clinical Trials: Genetic and Biomarker Disclosure

Joshua Grill
Associate Professor of Psychiatry and Human Behavior
Alzheimer’s Disease Research Center
Institute for Memory Impairments and Neurological Disorders
University of California, Irvine

Jason Karlawish
Professor of Medicine, Medical Ethics and Health Policy
Penn Neurodegenerative Disease Ethics & Policy Program
University of Pennsylvania
AD Prevention Trial Designs

1. Blinded enrollment – a proportion of participants who do not meet biomarker or genetic criteria are enrolled so that enrollment is not *de facto* disclosure of biomarker status. Those participants are non-randomly assigned to placebo and complete the entire protocol.

2. Transparent enrollment – only participants meeting biomarker or genetic criteria are enrolled and randomized to drug or placebo.
What Makes Clinical Research Ethical?

- Informed consent
- Independent review
- Social value
- Scientific validity
- Fair selection of subjects
- Favorable risk-benefit ratio
- Respect for enrolled subjects
## Special Issues in Informed Consent

<table>
<thead>
<tr>
<th>Blinded Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Procedural risks (blood draws, neuroimaging, lumbar puncture) without potential benefit</td>
</tr>
<tr>
<td>• Unwanted disclosure of risk status, e.g., adverse events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transparent Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Risk of learning risk status but not receiving effective therapy or even qualifying for the trial</td>
</tr>
<tr>
<td>• Unknown what proportion become impaired or what timeline will impairment occur?</td>
</tr>
</tbody>
</table>
Is the Requirement of Disclosure Coercion?

- Coercion: overt threat of harm to elicit compliance
- Undue influence: improper or inappropriate reward to elicit compliance
- Transparent enrollment is neither coercive nor does it offer undue influence
- Informed consent is critical to respect the autonomy of participants

To Be Ethical, Prevention Trials Must Be Feasible

• “...If persons who at baseline wish not to know their mutation [genetic/biomarker] status choose not to participate, then a majority of persons at risk for the condition would be excluded.”
Do you currently know if you are a carrier of a gene mutation that causes familial AD?

**Yes -or- No, but I want to know**

A1. Would you be interested in participating in a research study of an experimental drug to determine if that drug does (or does not) prevent or slow the development of familial AD?

- **No**
  - Check the reasons that apply
    - I don’t carry mutation
    - I would not risk side effects
    - Too much time and effort
    - Other
  - Stop here.

- **Yes**
  - A2. Would your opinion about such studies change if, instead of knowing for sure that you would receive the real drug, you had a 50% chance of receiving the real drug and 50% chance of receiving placebo?
  - A3. Would your opinion about such studies change if, instead of knowing for sure that you would receive the real drug, you had two chances of receiving the real drug and one chance of receiving placebo (that is, 2/3 of subjects receive the real drug and 1/3 receive a placebo)?
  - A4. Should you receive placebo during the study and there was the possibility of receiving active drug after the study was completed, would you now be interested in participating?

**No, I would prefer not to know at the present time**

B1. Would you change your mind if learning that you carried the gene mutation that causes familial AD gave you the opportunity to participate in a research study of an experimental drug to determine if that drug does (or does not) prevent or slow the development of familial AD?

- **No**
  - Check the reasons that apply
    - I don’t want to know if I will get AD
    - I do not want to participate in a study of an unproven drug
    - I would not risk side effects
    - Too much time and effort
    - Other
  - Stop here.

- **Yes**
  - B2. Would your opinion about such studies change if, instead of knowing for sure that you would receive the real drug, you had a 50% chance of receiving the real drug and 50% chance of receiving placebo?
  - B3. Would your opinion about such studies change if, instead of knowing for sure that you would receive the real drug, you had two chances of receiving the real drug and one chance of receiving placebo (that is, 2/3 of subjects receive the real drug and 1/3 receive a placebo)?
  - B4. Should you receive placebo during the study and there was the possibility of receiving active drug after the study was completed, would you now be interested in participating?
Genetic Testing in Autosomal Dominant AD Trials

- Already know status (40%)
- Wish to know status (15%)
- Do not know status (45%)
- Willing to find out to be in a trial (72%)
- Willing to participate (86%)

N=80 respondents from DIAN longitudinal study

Should Transparent Designs Be Implemented in DIAD?

- Hypothetical scenarios may not reflect actual behaviors
- Full informed consent and counseling (which were not part of the study) may reduce the desire to undergo testing
+ Taking action
+ Hope associated with research
+ Contributing to science

Thank You

• Participants are the heroes of the fight against Alzheimer’s disease
• Thank you!
• jgrill@uci.edu
The Continuum of Alzheimer’s Disease

Cognitive function vs. Years

Preclinical

Aging

MCI

Dementia

Sperling et al. 2011 Alz & Dem
A4 Study:Anti-Amyloid in Asymptomatic Alzheimer’s


Available as Open Access!
Telling others about your amyloid PET scan results

• Sharing the result
  – Who did you tell it to and how did they react?
  – Who didn’t you tell it to and why?

• How do you feel about your future?
Types of Stigma

- **Anticipated**
  - Expectations of experiencing prejudice and discrimination among the stigmatized

- **Received**
  - Overt behaviors of rejection and devaluation experiences of negative interactions

- **Enacted**
  - Behaviors of differential treatment by stigmatizers

- **Self**
  - Internalized acceptance of stereotypes and prejudice

- Pescosolido and Martin 2015
Anticipated stigma

- Anticipated stigma
  - Expectations of experiencing prejudice and discrimination among the stigmatized
  - Influences willingness to seek treatment by people diagnosed with mental illness (Vogel 2006; 2007)

- Anticipated stigma associated with amyloid imaging might challenge the wisdom of amyloid imaging if the goal is to encourage people to get treatment when one is available
  - Will receiving elevated amyloid result lead some people to see themselves as less worthy? Will others see them as less worthy?
Harkins et al. “Development of a process to disclose amyloid imaging results to cognitively normal older research participants.”

SOKRATES-I – amyloid disclosure
SOKRATES-II – ApoE disclosure
REVEAL-SCAN – impact of amyloid disclosure on cognition

Thank you!
JasonKarlawish@gmail.com
www.jasonkarlawish.com