Prevention Trials for Cognitive loss and Alzheimer’s Disease: Finding an invested patient population

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September 21, 2018
Societal Trends and Dementia

• 65+ age group: fastest growing segment of US population
• Increasing number of elders results in greater incidence and prevalence of AD
• Increasing longevity with disease
• 3- to 5-year period of mild but significant cognitive impairment precedes diagnosis
• Changing technology required for routine activities carries high cognitive demand
Trials for Prevention: Dementia and Cognitive Loss

• Dementia Prevention Trials:
  – Large and long

• Prevention of Cognitive loss:
  – Many improve
  – Treatment = greater improvement
Dementia Prevention Trial
Ginkgo Biloba vs. Placebo

>3000 enrolled

With CV risk

7 yrs; <2% change/yr

HR, 1.12 (95% CI, 0.94-1.33); P = .21

No. at risk
Placebo 1524 1485 1423 1342 1243 1148 792 81
G biloba 1545 1521 1458 1369 1254 1129 775 97

No. with incident dementia
Placebo 13 26 40 50 51 36 30
G biloba 10 26 47 66 60 40 27


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Pre-Diva Study

6 year cardiovascular intervention vs usual care trial
Age 70-78

@3500 participants
Risk of dementia: 1%/yr
No effect

Figure 2: Kaplan-Meier plot of cumulative incidence of dementia
To allow participants recruited early into the trial to continue follow-up until the 6-year assessment of the last participant was completed, the study was extended for participants randomised early (ie, in 2006–07). The hazard ratio (HR) refers to an analysis including all participants, up to 8 years of follow-up. The period beyond the planned 6-year follow-up, concerning few participants, is shaded.
FINGER STUDY RESULTS

Screened 2654 individuals and randomly assigned 1260

Figure 2. Change in cognitive performance during the 2 year intervention shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. E...

Very Small effect sizes

Both groups improved

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Lancet, Volume 385, Issue 9984, 2015, 2255–2263
Choosing the Right Participants

- Can we select for an “AD like” decline?
- How many do we need?
- How will we engage them?
- What will make them stay?
Apolipoprotein E for AD Risk

• Risk of AD increased by presence of e4
  – OR=3.2 (95% CI, 2.9–3.5) 1 allele
  – OR=11.6 (95% CI, 8.9–15.4) 2 allele

• Recommendation for use:
  – Only as within clinical work up in symptomatic cases
    » JAMA 1995
  – Reconsideration in prodromal or non-symptomatic?
    » Alzheimer & Dementia 2011
Preclinical Alzheimer’s Disease?

- Prevalence of PiB+ PET in HC
- Prevalence of plaques in HC (Davies, 1988, n=110)
  (Braak, 1996, n=551)
  (Sugihara, 1995, n=123)
- Prevalence of AD (Tobias, 2008)

~15 yrs

(Davies, 1988, n=110)  
(Braak, 1996, n=551)  
(Sugihara, 1995, n=123)
$^{18}$F-AV-45 Representative Images: Healthy Controls

Amyloid Negative HC

Amyloid Positive HC
Effect of amyloid
Decline in cognition over time

AIBL data
Challenges

• Disease modifying agents: benefit unlikely to be observable by patient

• Disease prevention vs. Clinical improvement
  – Unique/different populations require different recruitment and intervention strategies

• Technologies have a place but do not replace human touch

• Success or lack of it is not a secret and needs to be integrated into recruitment and retention strategies
Recruiting from Clinical Practice

• Perception of clinical population often overestimates recruitment

• Why?
  – Clinical bond may be a strong motivator for subject participation
  – Balance of “bond” and “bother”
  – Focus on inclusion criteria NOT exclusion criteria
Why True Eligible and Perceived Eligible Differs

• Commitment to experimental approach may not be high
• Procedures for standardization may have little clinical relevance to volunteers
• Concept of placebo is complex and not readily accepted by participants and families
• Adverse effect may be higher than recognized
Vulnerability: Relationship between Age and Adverse Drug Reactions

Overview

• Three studies
  – How do we select our message
    • Decision Making for brain donation
  – Retention
    • Why do they stay
  – Addressing burden with Home based assessment
    • Research satisfaction
Decision-Making Concerning Brain Donation in Alzheimer’s Research Among Research Participants and Their Families

Sewell M, Neugroschl J, Li C, Sano M.
Background

• To improve low rate of interest in brain donation
• N=97 (65 participants and 32 study partners)
• Previously declined or were unsure
• Open-ended questions about being approached
  – personal & general feelings about brain donation for research.
• Responses were qualitatively evaluated
  – Could be coded in > 1 category.
• Result:
  – 23% changed their status from “undecided” to “yes”
  – (25% of participants and 19% of study partners.)
## Reluctance and Concerns

<table>
<thead>
<tr>
<th>Type of response</th>
<th># Resp</th>
<th>P/SP</th>
<th>Sample responses:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need more information to share and talk with family</td>
<td>26</td>
<td>P 16</td>
<td>“I want to discuss it with my daughter.” “Tell me more about the process.” “I need to speak to my doctor and family members.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Religious prohibition</td>
<td>18</td>
<td>P 11</td>
<td>“I’m Jewish. The body is not supposed to be anything but whole.” “I don’t believe in it for religious reasons.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reluctance to talk about death</td>
<td>25</td>
<td>P 19</td>
<td>“....it’s not a pleasant conversation.” “The thought of dying is hard.” “I’m healthy; I’m not ready to make a decision.” “....very overwhelming to think about it....”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerns about body integrity</td>
<td>16</td>
<td>P 14</td>
<td>“I might need it.” “...I understand the benefits, but I don’t want my body altered.” “I want to die with everything I have....”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practical concerns</td>
<td>14</td>
<td>P 13</td>
<td>“How is it done? Will they drain my brain?” “How will you know that I have passed away?” “What if I’m not local?”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP 1</td>
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</tbody>
</table>
# Conviction and Decision

<table>
<thead>
<tr>
<th>Type of response</th>
<th># Resp</th>
<th>P/SP</th>
<th>Sample responses:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning on changing decision from no/undecided to &quot;Yes&quot;</td>
<td>22</td>
<td>P 13 SP 9</td>
<td>“Ready to sign up!”  “It will help my family ….know if my father really has AD.” “…We want to help future patients.” “I won’t be using my brain anyway after I die, so why not donate.’</td>
</tr>
<tr>
<td>Unknown or known negative wishes of the participant</td>
<td>6</td>
<td>P 0 SP 6</td>
<td>“My mother was …unlikely to donate when she was lucid.” “I never discussed it with my dad … feel he would have said yes…but since he cannot express his wishes I cannot make this decision for him.”</td>
</tr>
<tr>
<td>Too stressful</td>
<td>8</td>
<td>P 4 SP 4</td>
<td>“I just can’t see the point--it won’t help her. I just don’t want to put her--and I suppose myself--through that.” “…unnecessary grief for my children during an already tough time.”</td>
</tr>
<tr>
<td>Trust issues</td>
<td>2</td>
<td>P 1 SP 1</td>
<td>“If I were ever hospitalized and there was a complication, would they harvest my brain before my time was up?” “I’m concerned how well the brain will be used.”</td>
</tr>
</tbody>
</table>
What Drives the Decision

- Trust issues
  - Study Partner: 2%
  - Participant: 3%
- Too stressful
  - Study Partner: 6%
  - Participant: 13%
- Unknown or neg. wishes
  - Study Partner: 19%
- Change to Yes
  - Study Partner: 20%
- Practical
  - Study Partner: 20%
  - Participant: 3%
- Concerns: body
  - Study Partner: 22%
  - Participant: 6%
- Reluctant to talk re
  - Study Partner: 19%
  - Participant: 19%
- Religious prohib.
  - Study Partner: 22%
  - Participant: 17%
- More info/ talk w
  - Study Partner: 31%
  - Participant: 25%
Why They Stay: Understanding Research Participant Retention in Studies of Aging, Cognitive Impairment and Dementia

Judith Neugroschl¹, Mary Sano¹,², Xiaodong Luo¹, and Margaret Sewell¹,*

53 Participant
• 33 participants
• 20 Study Partners
2 or more visits to the center

“We are interested in identifying reasons why research volunteers like you choose to continue participation over time.... can you tell us your main reason(s) for staying?
# Voices and Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personally empowering</td>
<td>“Helps me take control of this</td>
</tr>
<tr>
<td>Obligation</td>
<td>“My wife makes me.” “I made a commitment to [my doctor].”</td>
</tr>
<tr>
<td>Financial</td>
<td>“It’s free care.” “Being paid is a perk.”</td>
</tr>
<tr>
<td>Value to my family</td>
<td>“(AD) runs in my family, so maybe this means my children will be free”</td>
</tr>
<tr>
<td>Altruism</td>
<td>“I want to help defeat the terrible problem of AD.” “If I can help, why not?” “Gives me pride to”</td>
</tr>
</tbody>
</table>
Study Partner and Participant responses in each category

- Personally empowering
- Obligation
- Financial
- Value to my family
- Altruism
- Value relationship with “experts”
- Concern about my health

Icahn School of Medicine at Mount Sinai
Challenges to recruiting for “Prevention”

• Messaging:
  – Convey the need to do the research (risk/fear)
  – Engage and empower people (ego?)
  – Inform of science & commitment (burden)
  – Maintain and retain (reinforcing)

• Listening:
  – What is the understanding
  – What is the perceived benefit
  – What is experienced burden
Assessing Clinical progression for Dementia Prevention Trials: Results from the HBA trial

Mary Sano
Susan Egelko, Michael C Donohue, Jeffrey Kaye, James Mundt, Chung-Kai Sun, Steven Ferris, Paul S. Aisen,
Home Based Assessment (HBA) trial

• Designed to develop efficient/effective methods for in-home evaluation
• Random assignment to 1 of 3 arms

Mail-in & Live Phone MIP
Interactive Voice Response IVR
Computer Kiosk MIP
Study Features

• Randomized study conducted at 27 site
• 581 non-demented participants completed in-person assessment and baseline HBA
• Assessed with brief instruments from domains important to transition to dementia
  -- Cognitive  -- Functional
  -- Global     -- Behavioral
  -- QOL        -- Pharmacoeconomic
• 4 Yr Follow up; face to face at start and end
Participant Flow

Screened
N = 713

Randomized
N = 640

Screen Fail
N = 73

Less education than randomized cohort

Randomization
N = 640

MIP
N = 211

IVR
N = 214

KIO
N = 215

Dropout
N = 59

Baseline
N = 581

Dropout
N = 4 (2%)

Dropout
N = 18 (8%)

Dropout
N = 37 (17%)

All pairwise comparisons significant

440

164

145

131
Demographic and Clinical Characteristics of Baseline Cohort: All Arms Combined

<p>| | |</p>
<table>
<thead>
<tr>
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>581</td>
</tr>
<tr>
<td>Age</td>
<td>80.9 (4.4)</td>
</tr>
<tr>
<td>Education</td>
<td>15.6 (2.9)</td>
</tr>
<tr>
<td>% Female</td>
<td>67</td>
</tr>
<tr>
<td>% Racial/ethnic minority</td>
<td>22</td>
</tr>
<tr>
<td>% Married</td>
<td>42</td>
</tr>
<tr>
<td>% History of hypertension</td>
<td>59</td>
</tr>
<tr>
<td>% Cardiovascular disease</td>
<td>74</td>
</tr>
</tbody>
</table>

No differences between baseline cohort and cohort that passed screening and discontinued after randomization
Who Refused and Why?

<table>
<thead>
<tr>
<th>Drop Out By Arm And Frequency</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP Annual</td>
<td>4 /105</td>
<td>4%</td>
</tr>
<tr>
<td>MIP Quarterly</td>
<td>0/106</td>
<td>0%</td>
</tr>
<tr>
<td>IVR Annual</td>
<td>7/107</td>
<td>6%</td>
</tr>
<tr>
<td>IVR Quarterly</td>
<td>11/107</td>
<td>10%</td>
</tr>
<tr>
<td>KIO Quarterly</td>
<td>16/109</td>
<td>15%</td>
</tr>
<tr>
<td>KIO Monthly</td>
<td>21/106</td>
<td>20%</td>
</tr>
</tbody>
</table>

Nature of complaints:
- Inconvenience of the equipment
- Too much time to participate
Dissatisfaction with Technologies

- “so ugly”
- “takes up so much room”
- “glow disturbs sleep”
- “interference of phone line”
- “static on line”
Stemming the Tide

- Drop out continued
- Research Satisfaction Survey at 18 mo into enrollment
- 8-item survey
- Open ended questions about preferences
Survey results

- Overall high satisfaction
- Highest among the low technology (MIP)
- Lowest among IVR
“The thing I have liked best about my experience in the study is . . .”

<table>
<thead>
<tr>
<th>Rank</th>
<th>#</th>
<th>%</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>18.3</td>
<td>volunteerism; contribute to AD research</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>17.7</td>
<td>challenged to improve own mental functional</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>16.8</td>
<td>positive interactions with study personnel</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>14.4</td>
<td>feedback on own mental functioning, whether reassuring or pointing to difficulties</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>9.2</td>
<td>fun, easy, filled time, interesting, engaging, liked test-taking in general, mental activity</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>8.0</td>
<td>education; increased awareness of what types of tasks are difficult with Alzheimer’s Disease and/or aging</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>5.5</td>
<td>convenience of being tested at home; no driving involved</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>4.6</td>
<td>limited time commitment, either in frequency or length of testing</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>1.8</td>
<td><em>nothing</em> mentioned regarding what was liked most</td>
</tr>
</tbody>
</table>
## mCSQ-8 Open-Ended Question #2: “What I liked least was . . .

<table>
<thead>
<tr>
<th>Rank</th>
<th>Count</th>
<th>%</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87</td>
<td>29.3</td>
<td>nothing</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>14.5</td>
<td>objected to particular tests: repeating numbers backwards &amp; story recall; finding tests “boring”</td>
</tr>
<tr>
<td>3.5</td>
<td>22</td>
<td>7.4</td>
<td>repetitiveness of each visit; some questioning validity, citing how much retained from prior visit</td>
</tr>
<tr>
<td>3.5</td>
<td>22</td>
<td>7.4</td>
<td>feeling inadequate, not liking being tested, nervous, aware that memory not what it once was</td>
</tr>
<tr>
<td>5.5</td>
<td>15</td>
<td>5.1</td>
<td>amount of time it took, especially if on a busy day</td>
</tr>
<tr>
<td>Rank</td>
<td>#</td>
<td>%</td>
<td>Category</td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>104</td>
<td>39.4</td>
<td><em>nothing</em> to change</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>12.9</td>
<td>change test items, eg., have alternate form</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>4.5</td>
<td>more personal contact with staff or fellow seniors</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>4.2</td>
<td>give us feedback, instruct us on how to improve our memory</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>3.4</td>
<td>change specific tests that are not enjoyed (story recall, #s backwards)</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>2.7</td>
<td>change the avatar (computer and audio tester), experienced as overly stern</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>2.7</td>
<td>improve the technical aspect of equipment used, eg, size, ugliness, etc.</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>2.7</td>
<td>allow testee to fastforward through listening to their own baseline account of their level of functioning (CGI)</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>2.7</td>
<td>change aspects of the vitamin-taking</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>2.7</td>
<td>improve flaws specific to the KIO operating system, requiring maintenance visits for breakdowns</td>
</tr>
</tbody>
</table>
Comparing Technologies

• No complaints:
  – MIP arm 48%
  – IVR arm 27%
  – KIO arm 15%

• Dislike of arm specific procedures:
  – KIO arm 35%
  – IVR arm 8%
  – MIP arm 4%
### Estimating Yield

**Lessons from SPRINT**

*Ramsey et al 2016*

#### Greater than or Equal 75

<table>
<thead>
<tr>
<th>Source</th>
<th># Screened</th>
<th># Randomized</th>
<th>Ratio</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass Mail</td>
<td>1726</td>
<td>1194</td>
<td>69%</td>
<td>44%</td>
</tr>
<tr>
<td>Media</td>
<td>203</td>
<td>116</td>
<td>57%</td>
<td>4%</td>
</tr>
<tr>
<td>Staff Referrals</td>
<td>1402</td>
<td>1036</td>
<td>74%</td>
<td>38%</td>
</tr>
<tr>
<td>Brochures</td>
<td>608</td>
<td>395</td>
<td>65%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3756</strong></td>
<td><strong>2636</strong></td>
<td><strong>70</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

#### LESS THAN 75

<table>
<thead>
<tr>
<th>Source</th>
<th># Screened</th>
<th># Randomized</th>
<th>Ratio</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass Mail</td>
<td>3098</td>
<td>1808</td>
<td>58.4</td>
<td>27</td>
</tr>
<tr>
<td>Media</td>
<td>1041</td>
<td>584</td>
<td>56.1</td>
<td>7</td>
</tr>
<tr>
<td>Staff Referrals</td>
<td>5145</td>
<td>3450</td>
<td>67.1</td>
<td>51</td>
</tr>
<tr>
<td>Brochures</td>
<td>1584</td>
<td>921</td>
<td>58.1</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10,692</strong></td>
<td><strong>6725</strong></td>
<td><strong>61.1</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

*Older cohort accurately identified by referral; but less likely to be referred*

*Older cohort 57% less likely to be recruited from media*
Conclusions and Considerations

• Participation is driven by many things, but mostly altruism
• Hesitation is driven by lack of information, understanding or conviction of value
• Sometimes no is no
  – Religious and cultural beliefs, and experience are strong and may be immutable .... Move on!
Conclusions and Considerations

• Retention is about delivering
• Clear preference for interpersonal over technology
  – Staff
  – Requests to meet others
• Asking about satisfaction improves participation
• Asking before we begin may be even better
**Why Clinical Research Participations?**

<table>
<thead>
<tr>
<th>Clinicians</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low referrals, delay new diagnostics, and treatments</td>
<td>• Standardized evaluations as baseline</td>
</tr>
<tr>
<td>• Mutual referral relationships</td>
<td>• Access to up-to-date research initiatives</td>
</tr>
<tr>
<td>– Tertiary care research centers need referral options</td>
<td>• Potential for earliest access to medications</td>
</tr>
<tr>
<td>– Enhance practice credibility</td>
<td>• Support for family and friends</td>
</tr>
<tr>
<td></td>
<td>• Contribution from self to family, society***</td>
</tr>
</tbody>
</table>
Whose job to support research

• Clinicians
  – Know how to refer to research,

• Volunteers (w or w/o disease)
  – Discuss with your family
  – Support the decision, be a study partner

• Everyone
  – Support public funding
  – Make your contribution
Not all studies for all participants

• Inclusion criteria:
  – Insure safety
  – Limitations by age co-morbidities other medications
  – Insure the ability to measure efficacy
  – Hearing / visual difficulties make

• How to Choose:
  – Select by interest
  – Work with those you trust
  – Be honest about how much you can do
  – Ask questions

Remember, you can always change your mind