Methods for Studies in Preventing Cognitive Loss and Dementia

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May 2, 2014
Overview

• Review State of the Science
• Describe Home Based Assessment
• Describe Research Satisfaction
• Introduce the A4
• Discuss Challenge of recruitment
• Insufficient evidence to support... use of pharmaceutical or dietary supplements to prevent cognitive decline or AD
• Promising research is under way (e.g. antihypertensive medications, omega-3 fatty acids, physical activity, and cognitive engagement)
Dementia Prevention Trial
Ginkgo Biloba vs. Placebo

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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Supplement Benefit? Only in those with low intake?

- MIDAS study
  - AAMI
  - Low omega 3 diet
  - Treated with DHA
  - Benefit in learning

*Docosahexaenoic Acid – DHA*
Mediterranean Diet and Dementia
Small but significant benefit in overall cognition
Home Based Assessment

• Develop efficient/effective methods for Primary Preventions Trials in dementia using new technologies

• Will Home Based Assessment (HBA) improve:
  • Recruitment of diverse elders?
  • Retention and reduce study costs?
  • Participation of those who find clinic-based assessment interferes with lifestyle?

• Aims:
  • Establish feasibility of HBA
  • Assess acceptability and efficiency of new methods of assessment
Proposed Technologies and Domains

• Mail In Administration & “tester administered” phone-based cognitive assessment (MIP)

• Telephone Assessment, automated presentation with vocal and key pad response (IVR)

• Computerized Assessment for presentation and response capture (KIO)

• Cognitive

• Functional
  – IADL
  – Performance-based Medication Compliance****

• Global

• Behavioral

• Quality of Life

• Pharmaco-economic
Study Design

Subjects

Randomized to Home-Based Assessment Technologies

Procedures

600 Non-Demented Community dwelling “real world” Elderly (≥75) 20% minority
In-Person Baseline Evaluation

Mail-in and Telephone Cognitive Battery Written Med diary (N=200)

Automated Telephone Assessment Phone Med diary (N=200)

Computerized Assessment & Medtracker (N=200)

4-Year Follow-Up Period

25% Receive an In-Person Evaluation
In-Person Diagnostic Evaluation Upon Trigger

All Receive In-Person Evaluations at 4-Year Endpoint
Participant Flow

Screened
N = 713

Screen Fail
N = 73

Randomized
N = 640

MIP
N = 211

IVR
N = 214

KIO
N = 215

Less education than randomized cohort

Randomization
N = 640

Dropout
N = 59

All pairwise comparisons significant

Baseline
N = 581

Dropout
N = 4 (2%)

Dropout
N = 18 (8%)

Dropout
N = 37 (17%)

N = 207

N = 196

N = 178
## Demographic and Clinical Characteristics of Baseline Cohort: All Arms Combined

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>581</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td>80.9 (4.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range = 75 – 98</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td>15.6 (2.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range = 0 – 20</td>
</tr>
<tr>
<td><strong>% Female</strong></td>
<td></td>
<td>67</td>
</tr>
<tr>
<td><strong>% Racial/ethnic minority</strong></td>
<td></td>
<td>22</td>
</tr>
<tr>
<td><strong>% Married</strong></td>
<td></td>
<td>42</td>
</tr>
<tr>
<td><strong>% History of hypertension</strong></td>
<td></td>
<td>59</td>
</tr>
<tr>
<td><strong>% Cardiovascular disease</strong></td>
<td></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>MIP Annual</th>
<th>4 /105</th>
<th>4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP Quarterly</td>
<td>0/106</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>IVR Annual</td>
<td>7/107</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>IVR Quarterly</td>
<td>11/107</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>KIO Quarterly</td>
<td>16/109</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>KIO Monthly</td>
<td>21/106</td>
<td>20%</td>
<td></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”
## Efficiency

<table>
<thead>
<tr>
<th></th>
<th>IVR</th>
<th>KIO</th>
<th>MIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to Baseline</td>
<td>39.2 (25.8)</td>
<td>55.7 (42.3)</td>
<td>33.5 (25.5)*</td>
</tr>
<tr>
<td>Training Time</td>
<td>39.1 (20.6)</td>
<td>76.7 (60.1)</td>
<td>25.6 (15.2)*</td>
</tr>
<tr>
<td>Preparation Time</td>
<td>24.0 (20.6)</td>
<td>141.4 (140.8)</td>
<td>18.6 (17.1)*</td>
</tr>
<tr>
<td>Time at Baseline w/o Testing</td>
<td>11.1 (16.8)</td>
<td>73.4 (235.6)</td>
<td>8.44 (23.77)*</td>
</tr>
<tr>
<td>Testing time</td>
<td>NA</td>
<td>NA</td>
<td>31.2 (12.8)</td>
</tr>
<tr>
<td>Total Time</td>
<td>72.0 (37.7)</td>
<td>280.4 (314.5)</td>
<td>79.1 (39.0)*</td>
</tr>
</tbody>
</table>

*P<0.001

- Longer time from Screen to Baseline for KIO
- Longer Training time for KIO and IVR
- Longer Preparation Times for KIO
Summary/Considerations

• HBA trial enrolled a diverse, elderly cohort
• High technology assessment methods
  – Acceptability not affected by subject demographic and clinical characteristics
  – Require more time at study initiation
• Inconvenience of equipment and assessment frequency associated with non-participation
• Continued erosion of participation from technology arms
Research Satisfaction

• Can we maximize participation by engaging subjects by asking for feedback?

• Adapted the Client satisfaction Survey
  – Structured item, multiple choice answers
  – Open ended questions:
    • What do you like best
    • What do you like least
    • What would you change

• Limitation: Could only ask those who stayed
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mCSQ</strong>&lt;br&gt;<strong>Multiple Choice Items</strong></td>
<td></td>
</tr>
<tr>
<td>(1) How would you rate the quality of the tests you have received during your participation in the study?</td>
<td></td>
</tr>
<tr>
<td>(2) What has been your experience of being tested?</td>
<td></td>
</tr>
<tr>
<td>(3) To what extent has our research program met your expectations?</td>
<td></td>
</tr>
<tr>
<td>(4) If a friend were to inquire about this evaluation research program, would you recommend our research program to him or her?</td>
<td></td>
</tr>
<tr>
<td>(5) How satisfied are you with the amount of help you have received?</td>
<td></td>
</tr>
<tr>
<td>(6) Has your participation in the research testing helped you to keep mentally sharp?</td>
<td></td>
</tr>
<tr>
<td>(7) Has your participation in the research testing changed your attitude about the new technologies you were asked to use during the study?</td>
<td></td>
</tr>
<tr>
<td>(8) If you had a chance to redo your decision to participate in this research program, do you think you would choose to participate?</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: mCSQ-8 Open-Ended Question #1: “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>16</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>nothing mentioned regarding what was liked most</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>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>6.5</td>
<td>15</td>
<td>5.1</td>
<td>KIO computer glitches</td>
</tr>
<tr>
<td>7.5</td>
<td>13</td>
<td>4.4</td>
<td>lack of feedback or follow-up</td>
</tr>
<tr>
<td>7.5</td>
<td>13</td>
<td>4.4</td>
<td>problem with how KIO test was designed, methodology, etc.; found design annoying or limited performance (e.g., left-handed person complained about KIO Trails hand covering items), arthritis, tremors, vision, etc.</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>3.4</td>
<td>coordination a problem, e.g., getting calls returned by staff; scheduling difficulties, keeping track of follow-up calls</td>
</tr>
</tbody>
</table>
Research: Taking the next step

• Prevent cognitive loss & dementia

• A4 *
$^{18}$F-AV-45 Representative Images: Healthy Controls

Amyloid Negative HC

Amyloid Positive HC
Cognition in Aβ Pos vs. Neg in HC > 70 years old

Florbetapir (18F AV-45) Phase II Study

Sperling R et al Neurobiology of Aging 2012
Anti-Amyloid treatment in Asymptomatic AD – The A4 Trial

• Older individuals (ages 65-85)
• Normal thinking and memory function
• Presence of amyloid on imaging
• May be at risk for developing Memory Loss
• Treatment with Solanezumab or placebo to reduce the rate of memory decline
Challenge of A4

• Non-impaired individuals learn amyloid status
  – Diversity recruitment goal: recruit 1 in 5 *
  – If positive enter a 4 year trial
  – Monthly infusions, 6 month assessments
  – If negative: for how long?

• Strength: Non-impaired. capable to consent

• Challenge: Defining non-impaired in a diverse population *
Using the Best Information to Screen

<table>
<thead>
<tr>
<th>Cognitive Tests</th>
<th>Spanish N=300</th>
<th>English N&gt;2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Recall</td>
<td>11 (3.8)</td>
<td>13.9 (3.9)</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>9.3 (4.1)</td>
<td>12.6 (4.4)</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.9 (2.3)</td>
<td>29.0 (1.3)</td>
</tr>
</tbody>
</table>

Need for greater participation to establish “normal performance”
Considerations

• Lifestyle changes and risk reduction benefits are likely to be small or already achieved
• Pharmacologic interventions maybe required
• Designing effective trials require participant engagement which is premised on
  – Altruism, not necessarily efficacy
  – Desire of human interaction
• Progress will require much higher engagement, particularly from diverse populations
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
### 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>