Research Registries to Accelerate Enrollment in Alzheimer’s Trials

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If I have seen further, it has been by standing on the shoulders of giants*

Jessica Langbaum
& her Alzheimer’s Prevention Registry Team

*Sir Isaac Newton
One needs to engage an extraordinary number of people to enroll a sufficient number of eligible participants in AD trials

AD trials face a narrow, rate-limiting screening & enrollment funnel
- Need to screen **tens of thousands** to identify the eligible thousands
- Screen failure rates as high as 85%

93% of sites fail to meet their enrollment goal in the originally stated timeline
85-90% of all trials (not just AD) experience delays in recruitment & enrollment
30% of all trials fail to meet their enrollment goals
Current Recruiting Models Cannot Supply Enough AD Trial Participants*

To recruit the estimated 4,500 participants needed in 2016, nearly 7 million people should be contacted.

- 6,750,000 Participants
- 675,000 Participants Referred
- 27,000 Participants Screened
- 22,500 Participants Needed

10% referred to site
4% screened
20% drop-out
80% screen fail

*courtesy of GAP Foundation
Why a Registry?

- Able to reach thousands of interested individuals for a potential study
- If eligible, able to re-contacted later for a different study
- Potential to accelerate trial enrollment & perhaps enhance retention
- Potential to reduce screen failure rate
- Online registry can complement & enhance local, grassroots recruitment
- Depending on registry’s design, may be able to leverage run-in data for trial
General Public Perceptions about Research Registries

• We analyzed nearly 19,000 conversations from 84 online destinations (websites, blogs, forums, etc.) to try to understand the primary motivators & barriers to join a registry & participate in a trial
  – Drivers: helping future generations, driving science forward, taking control of their own lives
  – Barriers: concerns regarding privacy, data security, who is “behind” the program
• Meantime, we continue to learn from API & other programs about factors that influence a registry participant’s willingness to participate in a trial
  – e.g., their proximity to a trial site
Recruitment Registries: Examples in the US*

- **National Registries**
  - Alzheimer’s Prevention Registry
  - Brain Health Registry
  - DIAN Expanded Registry
  - GeneMatch
  - HealthyBrains
  - ResearchMatch
  - TrialMatch

- **Local / Regional Registries**
  - Butler Alzheimer’s Prevention Registry
  - Penn Memory Center Brain Health Research Registry
  - Rhode Island AD Prevention Registry
  - UC Irvine Consent-to-Contact Registry
  - Wisconsin ADRC Registry

Registries are listed in alphabetical order. Other registries may be found on clinicaltrials.gov
## Tiers of Engagement in Several National Registries

<table>
<thead>
<tr>
<th>Requirements / Engagement Tiers</th>
<th>Alzheimer’s Prevention Registry</th>
<th>Brain Health Registry</th>
<th>GeneMatch</th>
<th>TrialMatch</th>
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<tr>
<td>DNA multiple genetic tests</td>
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<td>GenePool substudy</td>
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<tr>
<td>DNA storage for future tests</td>
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<td>GenePool substudy</td>
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Recruitment Registry Example: the Alzheimer’s Prevention Registry

• Began with API’s interest in enrolling cognitively unimpaired APOE4 homozygotes in a prevention trial
• Currently helping to recruit for 39 studies, primarily in US
• Offers several email subscriptions services: monthly newsletter, community events, study opportunities
• ~86,000 adults age 60+ receive our emails
• highly engaged, average 30-40% email open rates
• not representative of US population, predominately white women (focus of pending R01 grant)
Recruitment Registry Example: GeneMatch

• GeneMatch has enrolled >90,000 cognitively healthy 55-75 year olds in the US
• CLIA-certified APOE genotypes in >62,000

<table>
<thead>
<tr>
<th>Age Group</th>
<th>% of Total Number of Referrals</th>
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<td>55-59</td>
<td>35%</td>
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<tr>
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<td>57-69</td>
<td>20%</td>
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<tr>
<td>60-69</td>
<td>15%</td>
</tr>
<tr>
<td>60-75</td>
<td>10%</td>
</tr>
</tbody>
</table>

Genotype / Age Group

- e2/e2
- e2/e3
- e2/e4
- e3/e3
- e3/e4
- e4/e4

- % of Total Number of Referrals
- % of Total Number of Participants

API Colombia Registry

- Led by Francisco Lopera & his Grupo Neurociencias de Antioquia (GNA) in partnership with API
- Includes more than >5,800 persons, 8-75 years of age, from the largest ADAD kindred, including ~1200 PSEN1 E280A mutation carriers--& 6 homozygotes
  - e.g., plasma NfL study in more than 1,100 carriers & 1,100 age & sex-matched non-carriers.
- Blood samples & genetic testing in all; clinical & cognitive assessments in most
- Sole recruitment mechanism for the API ADAD Colombia Trial
- Supports observational, genetic, brain imaging, fluid biomarker & neuropathological studies
- Potential to extend to other autosomal dominant AD & CADASIL kindreds
- Foundation for other observational, biomarker, treatment & prevention studies

Rios-Romenets et al, J Prev Alzheimers Dis 2018
Future Direction: Amyloid Blood Test Screening Program

- Building off the GeneMatch model, we have been exploring the development of an Aβ blood test screening program
  - To accelerate & improve the efficiency of enrolling Aβ+ participants (including APOE4 non-carriers) in prevention trials
  - To provide a resource of blood samples & brain imaging data for the further evaluation of different Aβ tests (including a subset of persons who with a negative blood test)
  - To provide a foundation for the potential use of Aβ blood tests as a screening tool in the clinical setting
Challenges to the development of recruitment registries – The tip of the iceberg!

• Even if you build it, they may not come! Requires considerable advertising & outreach to enroll participants
  – Attracting healthy people
  – Limited diversity. Most respondents are white, educated & female (though some can be gait-keepers for other eligible participants)

• One size does not fit all: best practices are limited in terms of their generalizability
  – How much data do you collect at signup? Different thresholds of commitment at entry yield different populations & results

• Requires a high level of customer service & continued engagement with enrollees
  – To date, most registries are only in English

• Navigating a complicated regulatory / legal landscape to...
  – Collect personally identifiable information (PII) & protected health information (PHI)
  – Connect people to studies & provide metrics of study enrollment success
  – Collect DNA & perform genetic tests

• Funding
  – NIH does not support “infrastructure” for registries, but supports cohort studies

• Creating the IT infrastructure is time consuming & expensive
  – No “out of the box” solution

• Website design matters
Future Directions

• Gain a deeper understanding of motivators & barriers
  – particularly for under-represented racial, ethnic & male groups
• Monitor & continue to optimize our registries’ performance & impact
  – including their impact on study engagement, enrollment, & retention
• Partner with Ethics Committees / IRBs:
  – work towards using more motivational, inspirational language to encourage enrollment, particularly for healthy adults & under-represented groups
  – find seamless mechanisms to share participant PII/PHI
• Incorporate new features & technologies to online registries to promote engagement, retention & data collection
  – e.g., text messaging, wearable technologies, etc
• Translate registries to other languages
  – Would require multilingual staff for registries, study sites
  – Not just the websites, but also all retention/engagement emails, etc
• Work with & support other registries
• Challenge: How to extend to other countries
  – For instance, how to address European Union Global Data Protection Requirements (GDPR) & other regulatory & language requirements
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