Challenges in the Design of Premanifest HD Trials

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Acknowledgments

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Disclosures

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- Paid consulting: Roche, Wave, Vaccinex, Triplet

- Other support: CHDI, National Institutes of Health (NIH)
### Variables

<table>
<thead>
<tr>
<th>Level of Measurement</th>
<th>Continuous&lt;sup&gt;1-5&lt;/sup&gt;</th>
<th>Categorical (Event)&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single</strong></td>
<td>TMS, TFC, SDMT, Stroop</td>
<td>DCL = 4, TFC &lt; 13</td>
</tr>
<tr>
<td><strong>Multiple</strong></td>
<td>cUHDRS</td>
<td>DCL = 4 OR TFC &lt; 13</td>
</tr>
</tbody>
</table>

- **TMS**: UHDRS Total Motor Score
- **TFC**: UHDRS Total Functional Capacity
- **DCL**: UHDRS Diagnostic Confidence Level
- **cUHDRS**: weighted composite of TMS, TFC, Symbol Digit, Stroop Word<sup>1-5</sup>

cUHDRS, composite UHDRS; DCL, diagnostic confidence level; SDMT, symbol digit modality test; TFC, total functional capacity; TMS, total motor score; UHDRS, Unified Huntington Disease Rating Scale.

Premanifest Randomized Controlled Trial

- Parallel groups (treatment, placebo)
- Must demonstrate change in untreated patients\(^1\)
  - Deflection of natural course (continuous variable)
  - Delay of landmark event (categorical variable)
  - Determines effect size for power calculations

What Changes and When?\(^2\)

- Enroll-HD
- CAG = 42
- N = 1001 longitudinal cases
- Clinical variables

CAG, cytosine-adenine-guanine.

Change of Clinical Variables Over Time

- Enroll-HD
- CAG = 42
- N = 1001
- 50% survival

SDMT 50% Effect Size


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Variability Increases With Age

Required Total Sample Size

- Two groups
- Equal size
- 5-year trial
- 6-month visits
- \( \alpha = .05 \)
- Two-sided test
- Power = .80

CAP, CAG age product; PIN, prognostic index for HD normed.

Required Total Sample Size at Age 42 Years
(CAG = 42, CAP = 350, PIN = -0.03)

### Enrichment Indexes Anchored to Motor Diagnosis

<table>
<thead>
<tr>
<th>Type of Data</th>
<th>Cross-Sectional</th>
<th>Longitudinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAG + Age + Clinical</td>
<td>PIN (Long et al, 2017)</td>
<td>PING (Long et al, 2018)</td>
</tr>
</tbody>
</table>

- CAP: CAG-age product
- PIN: Prognostic index for HD normed
- PING: PIN with genetic information

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Premanifest gold-standard trial might be feasible

Major caveats

- End point must have relatively fast rate of change
- Enrich for critical period (not too early)
- Effect size must be substantial ($\Delta >25\%$)
- Trial length might have to be long (5 years or more)
- Accurate estimates of variance components are necessary
- Account for placebo effects and patient dropout
Progression-Free Survival
- Treatment to delay landmark event (Long et al, 2018)

Sequential Analysis
- Accrue subjects until definitive efficacy or inefficacy (Whitehead, 2005)

Bayesian Approaches
- Gain in the results for stakeholders (Miller et al, 2017)

Alternatives to Parallel Groups
- Delayed-start design (D’Agostino, 2009)

Thank you!
References


References


