Rigor, Reproducibility and Generalizability in ADRD Clinical Trials

A Biostatistics Perspective

Rema Raman, Ph.D.
Director of Biostatistics, Alzheimer's Therapeutic Research Institute (ATRI)
Lead, Biostatistics Unit, Alzheimer's Clinical Trials Consortium (ACTC)
October 12, 2019

ADC Directors Meeting, St. Louis
“... three things matter: the data, the methods used to collect the data (which give them their probative value), and the logic connecting the data and methods to conclusions. ...”

-- Brown, Kaiser and Allison

What is Scientific Rigor?

Interpretation of Results

Replication/Validation (Experimental Design)

Recognition of Error (Data Collection & Management)

Sound Statistical Analysis

Objectivity

Logic

Experimental Redundancy

Error Analysis

Intelectual Honesty

Scientific Rigor

Rigorous Process for Data Flow

Common Data Standards (CDA)

Data Monitoring

Governance

Quality Review

Data Sharing

ATRI/ACTC Biostatistics
Statistical Analysis Plan – Key Guidelines

• Multidisciplinary effort between the clinical investigator and the statistician
  • Ensures that the objectives and statistics are aligned
  • Eliminates/reduces bias and improves study quality

• Approved and finalized prior to blind break and analysis (maintains integrity of the research)

• Explicitly describes the alpha spending to ensure study wide Type I error rate

• Explicitly addresses assessment of missing data, imputation approaches and sensitivity analysis

• Clearly defines the ‘estimand’ (target of estimation) and ‘estimator’ (method of estimation) (NRC, ICH-E9)
  • Links study objectives, data and analysis
Futility Analysis

- Formal statistical approach
- Incorporates data obtained during the course of the study
- Does not compromise the validity/integrity of the study

Assesses the ability of a clinical trial to achieve its objectives
Stop trials that would not have shown statistical significance had they gone to completion

Pros:
- Efficient use of research resources
- Can eliminate ineffective treatments

Cons:
- Difficult to interpret negative findings
- Treatment effect biased downward
- Suboptimal use of limited resources: cannot answer the intended question

Futility analysis relies on amount of information available
For long trials, when most of the information is not available until close to the end, their utility should be carefully evaluated
What is Reproducible research?

Reproducible (Analytical)
Possible to reproduce the data analysis results, given the raw data, statistical analysis plan, protocol and data dictionaries

Replicable (Experimental)
Ability to duplicate the results of a prior study if the same procedures are followed but new data is collected

Take an approach at the start that the final product will be reproducible
Develop tools, processes and policies that facilitate reproducible research
Dynamic Documents and Auditable Processes
ATRI/ACTC Biostatistics Ecosystem

- S3 Buckets
  - Data
- ShinyApps.io
  - Data
- Study EDC Portals
  - Docs Tool
  - Data Tool
  - Meta data
  - Data
  - Reports
- Jenkins/Statbot
  - biostatproc.atrichub.org/jenkins
  - Study R packages
  - Reports
- External Groups
  - Data sharing (e.g. LONI)
  - EDC (e.g. LEADS)
  - Data
  - Code
- github.com/atrichub
- Box
  - Biostat > Bot > Botsync
  - Studies > Study Name > Trackers, Metrics, Reports
Open Data Sharing

Collaboration for Alzheimer’s Prevention: Principles to guide data and sample sharing in preclinical Alzheimer’s disease trials

Stacie Weninger\(^a\,*\), Maria C. Carrillo\(^b\,**\), Billy Dunn\(^c\), Paul S. Aisen\(^d\), Randall J. Bateman\(^e\), Joanne D. Kotz\(^f\), Jessica B. Langbaum\(^f\), Susan L. Mills\(^g\), Eric M. Reiman\(^f\), Reisa Sperling\(^g\), Anna M. Santacruz\(^e\), Pierre N. Tariot\(^f\), Kathleen A. Welsh-Bohmer\(^h\)

\(^a\)F-Prime Biomedical Research Initiative, Cambridge, MA, USA
\(^b\)Medical & Scientific Relations Division, Alzheimer’s Association, Chicago, IL, USA
\(^c\)Division of Neurology Products, U.S. Food and Drug Administration, Silver Spring, MD, USA
\(^d\)University of Southern California Alzheimer’s Therapeutic Research Institute, San Diego, CA, USA
\(^e\)Department of Neurology, Washington University, St Louis, MO, USA
\(^f\)Banner Alzheimer’s Institute, Phoenix, AZ, USA

- **Implemented for the A4 trial:**
  - A4 pre-randomization clinical data available on LONI (> 150 downloads since Jan 2019)

- **Approach for NIA’s ACTC and Alzheimer’s Association’s U.S. POINTER trial**
General Principles

• Open data sharing through data harmonization allows for improved governance and usability of data at a local, national and global level.

• Data harmonization is a collaborative process and the quantitative experts are key scientific collaborators in this effort.

• Development and availability of data standards should be established at the beginning of a research project or program, not at a later stage.

• Data harmonization provides an optimal infrastructure for collaborative initiatives.
What is Generalizability?

The results of a study apply in other contexts and populations that differ from the original one.
Selection Bias in ADRD Clinical Trials: ‘Internal’ Validity without ‘External’ Validity

<table>
<thead>
<tr>
<th>Internal Validity</th>
<th>External Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>accurate estimates of the effect of the intervention for the participants in the trial</td>
<td>relevant information about the effects in a particular target population (participants/treatments/outcome/setting)</td>
</tr>
</tbody>
</table>

Possible Reasons for failing to achieve external validity:

- Lack of specification of a target population when designing the trial
- Interest in target population somewhat different from the trial target population
- Difficulties recruiting a sample that is representative of a pre-specified target population
## Participant Demographics (Preclinical Studies)

<table>
<thead>
<tr>
<th></th>
<th>Registry</th>
<th>Observational Studies</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APT Webstudy</td>
<td>NACC - NC (N=14638)</td>
<td>ADNI3 - CN (N=490)</td>
</tr>
<tr>
<td>Age</td>
<td>65.2 (8.2)</td>
<td>72.8 (11.4)</td>
<td>73.7 (8.2)</td>
</tr>
<tr>
<td>Sex, % Female</td>
<td>73%</td>
<td>65%</td>
<td>58%</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>93%</td>
<td>78%</td>
<td>90%</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>2%</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Asian</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>American Indian</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Ethnicity, % Hispanic</td>
<td>2%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Education, &gt;12 y</td>
<td>95%</td>
<td>73%</td>
<td>93%</td>
</tr>
</tbody>
</table>

\(^1\) Pre-randomization, Elevated Amyloid  
* Includes Japan
## Participant Demographics (Dementia Studies)

<table>
<thead>
<tr>
<th></th>
<th>Observational Studies</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NACC - Dementia (N=17869)</td>
<td>ADNI3 - AD (N=90)</td>
</tr>
<tr>
<td>Age</td>
<td>75.9 (10.8)</td>
<td>78.1 (9.0)</td>
</tr>
<tr>
<td>Sex, % Female</td>
<td>52%</td>
<td>43%</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>83%</td>
<td>96%</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Asian</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>American Indian</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Ethnicity, % Hispanic</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Education, &gt;12 y</td>
<td>57%</td>
<td>88%</td>
</tr>
</tbody>
</table>
Challenges to D&I in Clinical Trials Recruitment

Conflict 1: Homogeneity versus Heterogeneity

Conflict 2: Enrollment versus Diversity
Final Thoughts

- Developing a research protocol, including the statistical methodology and approach, is a collaboration among the study leadership team (TEAM SCIENCE)

- Successful clinical trial/clinical study requires focus on rigor, reproducibility and generalizability

- Open data sharing with minimal restrictions allows external validation of study designs, outcomes and statistical models.

- Many unresolved issues in the field: need for futility analysis, open data sharing, diversity in study participants and patients, optimal statistical model.

- ACTC was established to foster rigor and quality in ADRD clinical trials research through collaboration

We look forward to continued and expanded collaboration between the ACTC Consortium and the ADC Program
Alzheimer’s Clinical Trials Consortium (ACTC)
The ACTC is a cooperative agreement between the NIA and the grantees institutions

Call for Ideas and Proposals

Eligibility: Anyone (academic or industry)
Studies: All Phases (Phase 1b-III)

Review Process:
• Contact ACTC to discuss proposed trial (actcinfo.org)
• Idea evaluated for mission relevance and feasibility by ACTC protocol feasibility and evaluation committees
• Formal vote by ACTC steering committee
• Approved investigator develops and submits a formal joint application to ACTC FOA.