Rigor, Reproducibility and Generalizability in ADRD Clinical Trials

A Biostatistics Perspective

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USC University of Southern California
Alzheimer's Therapeutic Research Institute

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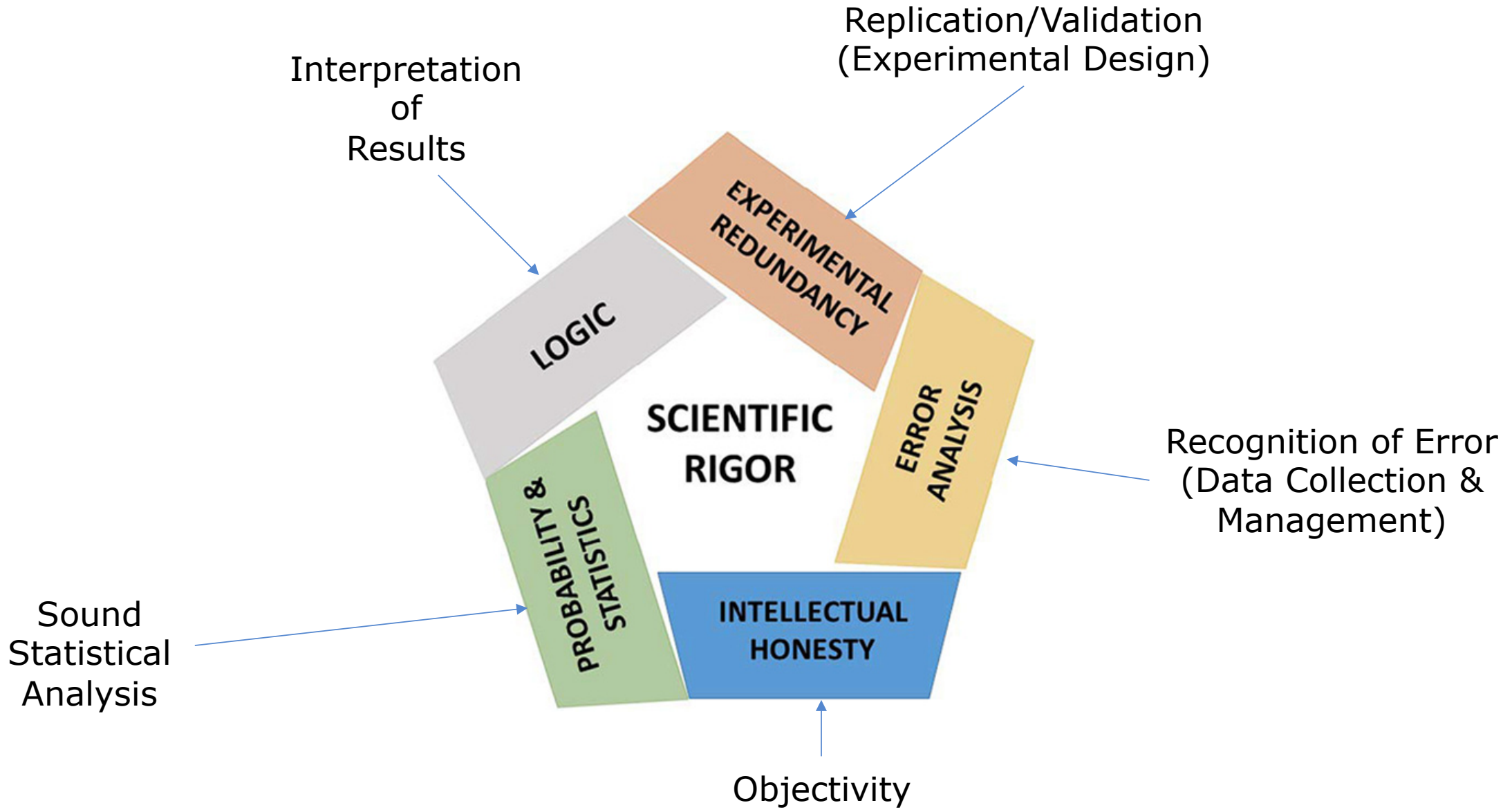
ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

"… 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

Brown, Kaiser and Allison. "Issues with data and analyses: Errors, underlying themes, and potential solutions", PNAS, 2018, 115(11): 2563:2570

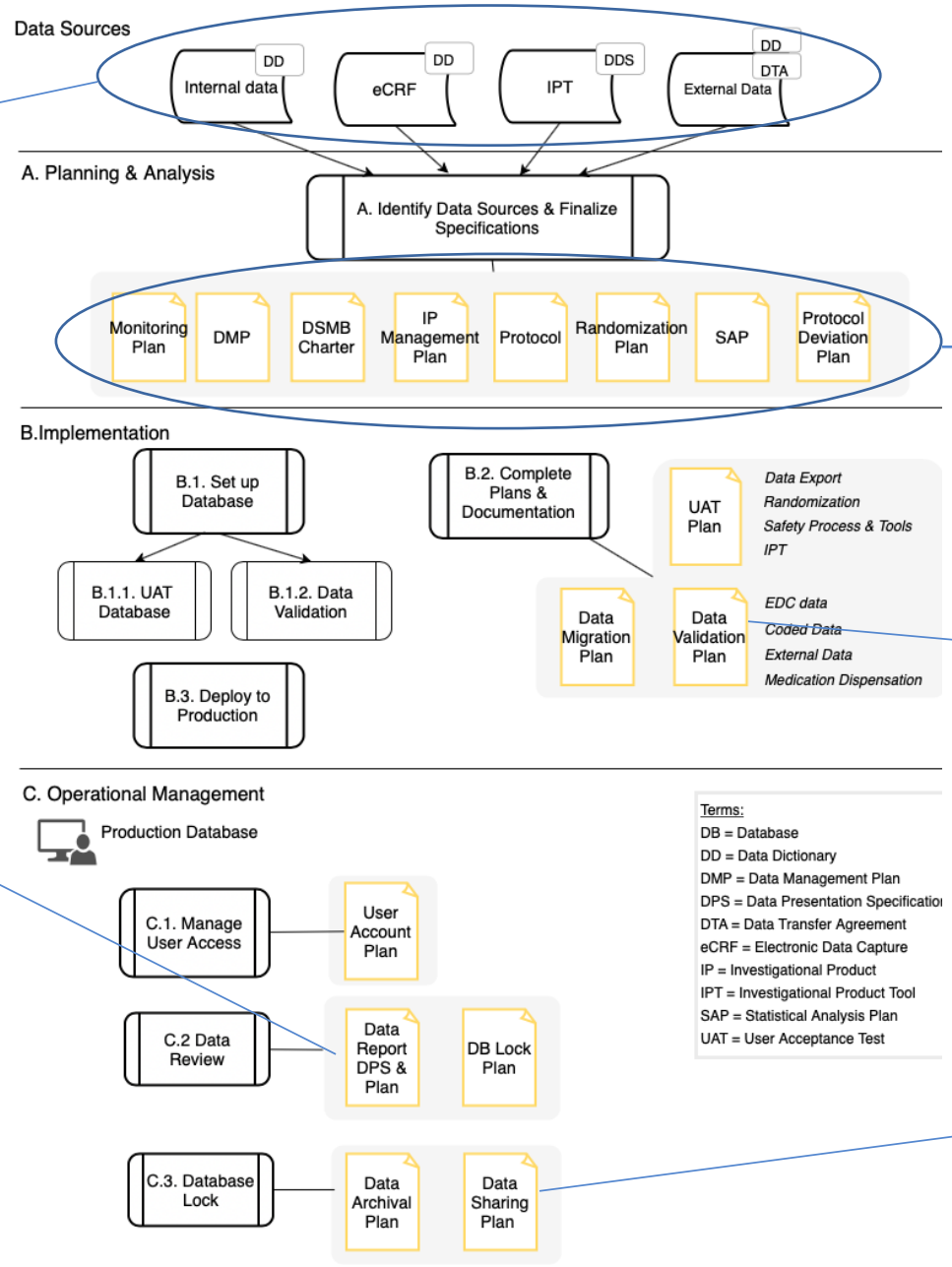
What is Scientific Rigor?



Casadevall A, Fang FC. 2016. Rigorous science: a how-to guide. mBio 7(6):e01902-16. doi:10.1128/mBio.01902-16.

Rigorous Process for Data Flow

Common Data Standards (CDA)



Governance

Data Monitoring

Quality Review

Data Sharing

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

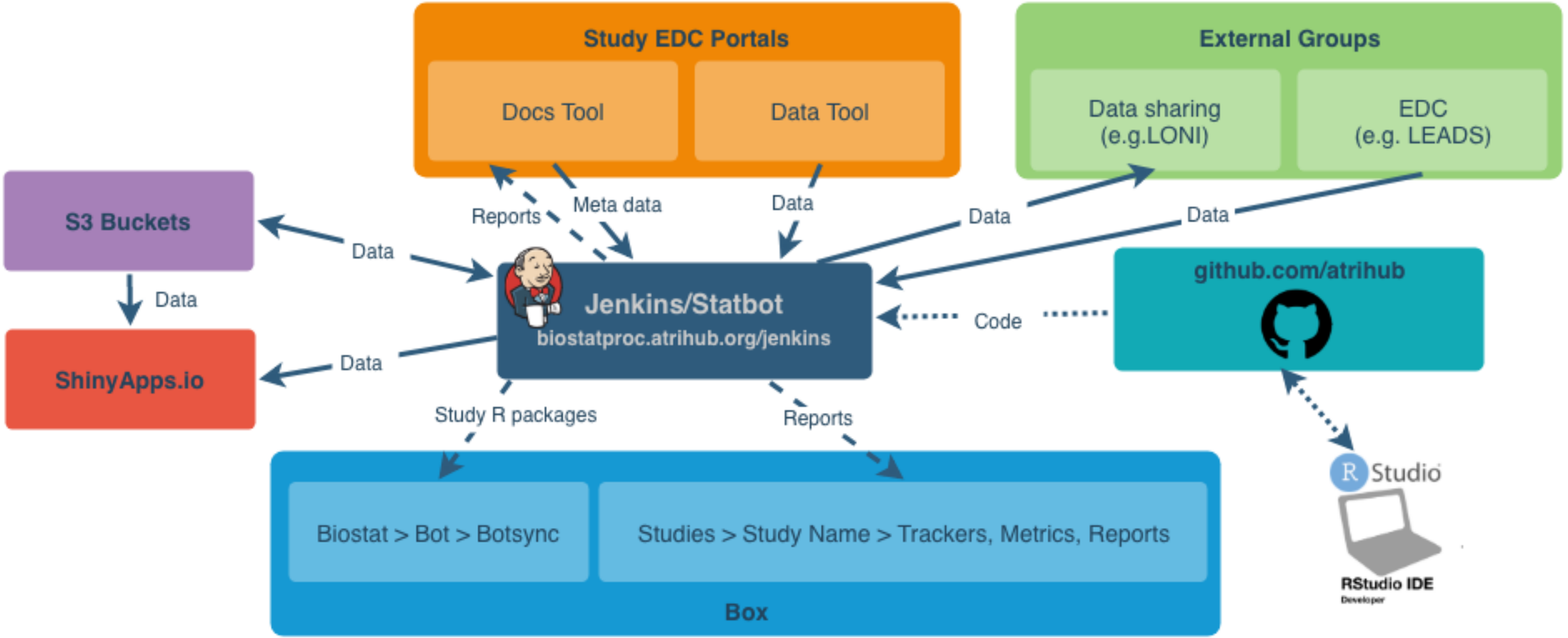
Replicable (Experimental)

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

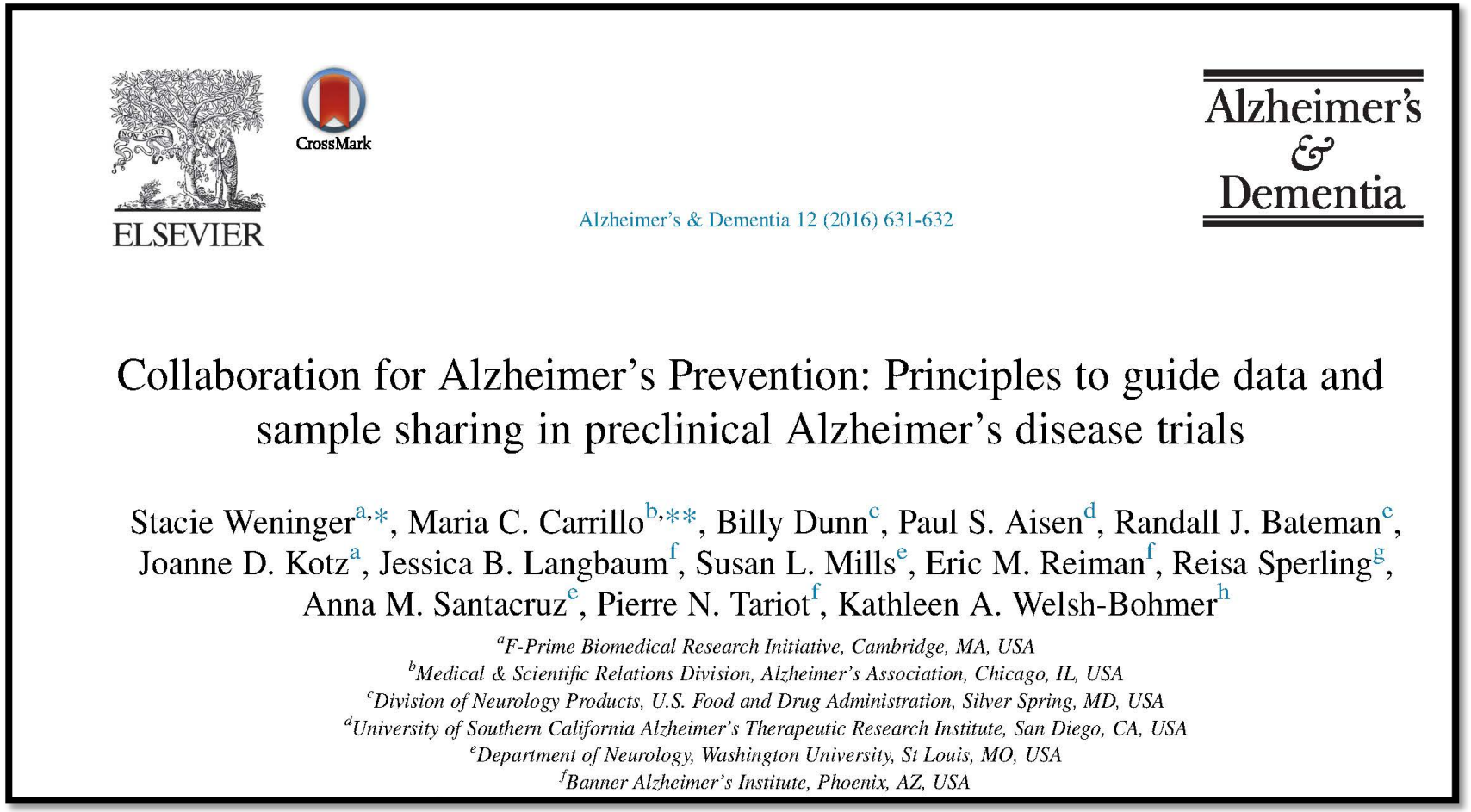
Take an approach at the start that the final product will be reproducible

Develop tools, processes and policies that facilitate reproducible research

Dynamic Documents and Auditable Processes
ATRI/ACTC Biostatistics Ecosystem



Open Data Sharing



ELSEVIER

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Alzheimer's & Dementia 12 (2016) 631-632

Alzheimer's & Dementia

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[a], Jessica B. Langbaum[f], Susan L. Mills[e], Eric M. Reiman[f], Reisa Sperling[g], Anna M. Santacruz[e], Pierre N. Tariot[f], Kathleen A. Welsh-Bohmer[h]

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- **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

Internal Validity	External Validity
accurate estimates of the effect of the intervention for the participants in the trial	relevant information about the effects in a particular target population (participants/treatments/outcome/ setting)

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)

	Registry	Observational Studies		RCT
	APT Webstudy	**NACC - NC (N=14638)**	**ADNI3 - CN (N=490)**	**A4[1] (N=1323)**
Age	65.2 (8.2)	72.8 (11.4)	73.7 (8.2)	72.1 (4.9)
Sex, % Female	73%	65%	58%	59%
Race, % White Black or African-American Asian American Indian Other	 93% 2% 1% <1% 3%	 78% 14% 3% <1% 4%	 90% 5% 2% <1% 2%	 94% 3% 2%* 1% -
Ethnicity, % Hispanic	2%	7%	5%	3%
Education, >12 y	95%	73%	93%	90%

[1] Pre-randomization, Elevated Amyloid

* Includes Japan

Participant Demographics (Dementia Studies)

	Observational Studies		RCT	
	NACC - Dementia (N=17869)	ADNI3 - AD (N=90)	FYN (N=159)	INI (N=289)
Age	75.9 (10.8)	78.1 (9.0)	71.0 (7.7)	71.0 (7.1)
Sex, % Female	52%	43%	45%	46%
Race, %				
White	83%	96%	94%	95%
Black or African-American	10%	1%	7%	3%
Asian	2%	2%	0%	2%
American Indian	<1%	0%	1%	<1%
Other	4%	1%	1%	0%
Ethnicity, % Hispanic	8%	2%	4%	3%
Education, >12 y	57%	88%	82%	86%

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.

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