Pre-registration:
A tool for enhancing rigor in your research

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Outline

- Why should you pre-register your study and/or analysis plan?
- What does it mean to “pre-register” your study and/or analysis plan?
- How do you pre-register your study and/or analysis plan?
  - Observational studies
    - Clinicaltrials.gov - for observational studies
    - Open Science Framework
  - Experimental/Intervention studies or Clinical trials
    - Clinicaltrials.gov
- Some questions you likely have about this
- A parable for why pre-registration matters for research on older adults

Transparency in data and code is the future of science

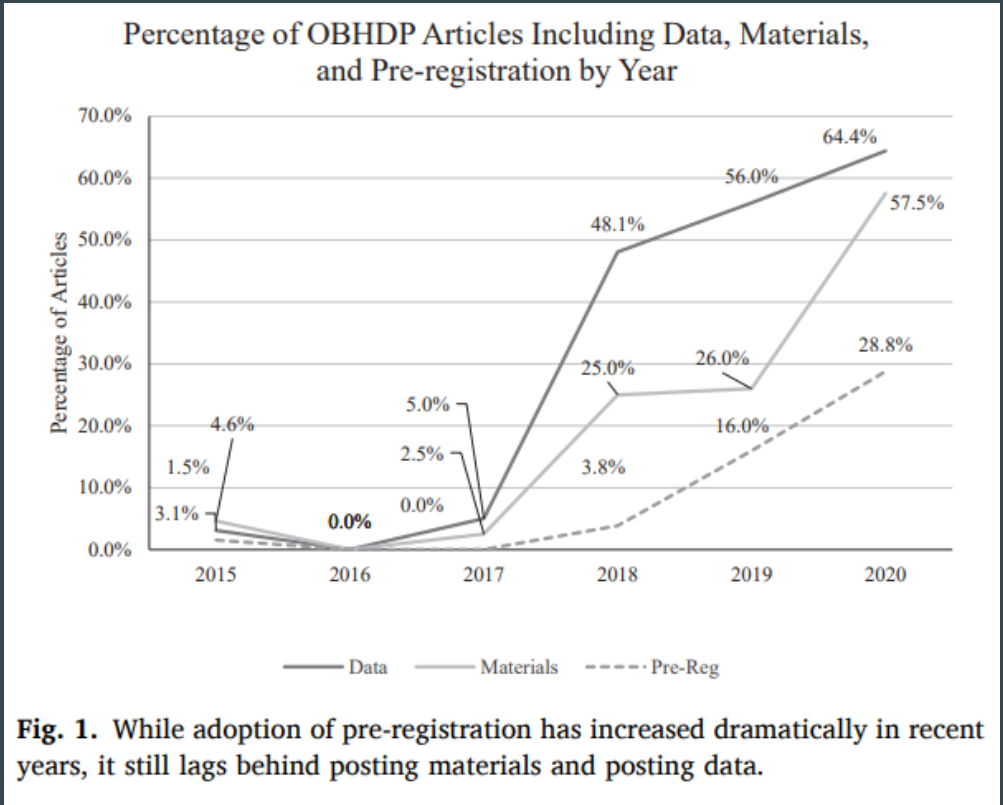


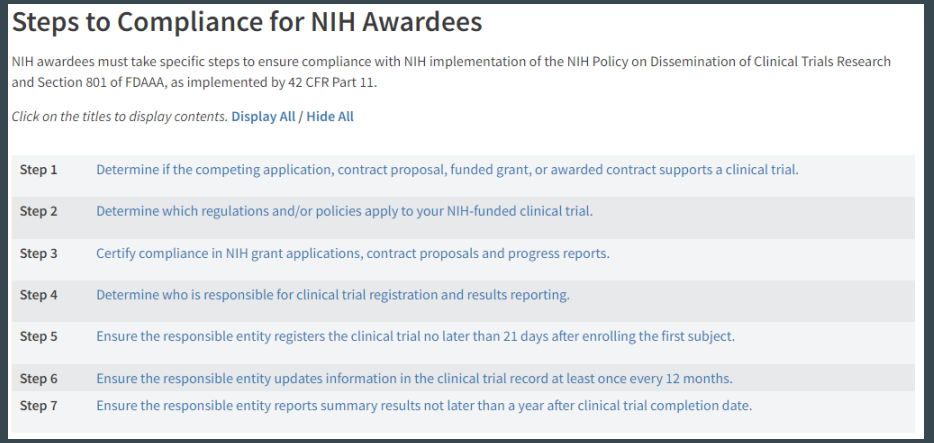
Fig. 1. While adoption of pre-registration has increased dramatically in recent years, it still lags behind posting materials and posting data.

*OBHDP: Organizational Behavior and Human Decision Processes (OBHDP) (Journal)

Why should you pre-register?

- It improves the rigor of science
  - Prevents “fishing expeditions” (p-hacking: selective reporting of statistically significant findings)
  - Provides upfront clarity about confirmatory/a priori vs. exploratory/post-hoc hypotheses
    - Should you really use a threshold of $p<0.05$ when you’ve already “tested” the hypothesis in exploratory data analysis?
  - Ensures null results are published
  - Helps others replicate your work

- You are required to as a condition of receiving NIH funding to conduct experimental research



Steps to Compliance for NIH Awardees

NIH awardees must take specific steps to ensure compliance with NIH implementation of the NIH Policy on Dissemination of Clinical Trials Research and Section 801 of FDAAA, as implemented by 42 CFR Part 11.

Click on the titles to display contents. **Display All / Hide All**

Step 1	Determine if the competing application, contract proposal, funded grant, or awarded contract supports a clinical trial.
Step 2	Determine which regulations and/or policies apply to your NIH-funded clinical trial.
Step 3	Certify compliance in NIH grant applications, contract proposals and progress reports.
Step 4	Determine who is responsible for clinical trial registration and results reporting.
Step 5	Ensure the responsible entity registers the clinical trial no later than 21 days after enrolling the first subject.
Step 6	Ensure the responsible entity updates information in the clinical trial record at least once every 12 months.
Step 7	Ensure the responsible entity reports summary results not later than a year after clinical trial completion date.

What, exactly, are you “pre-registering”?

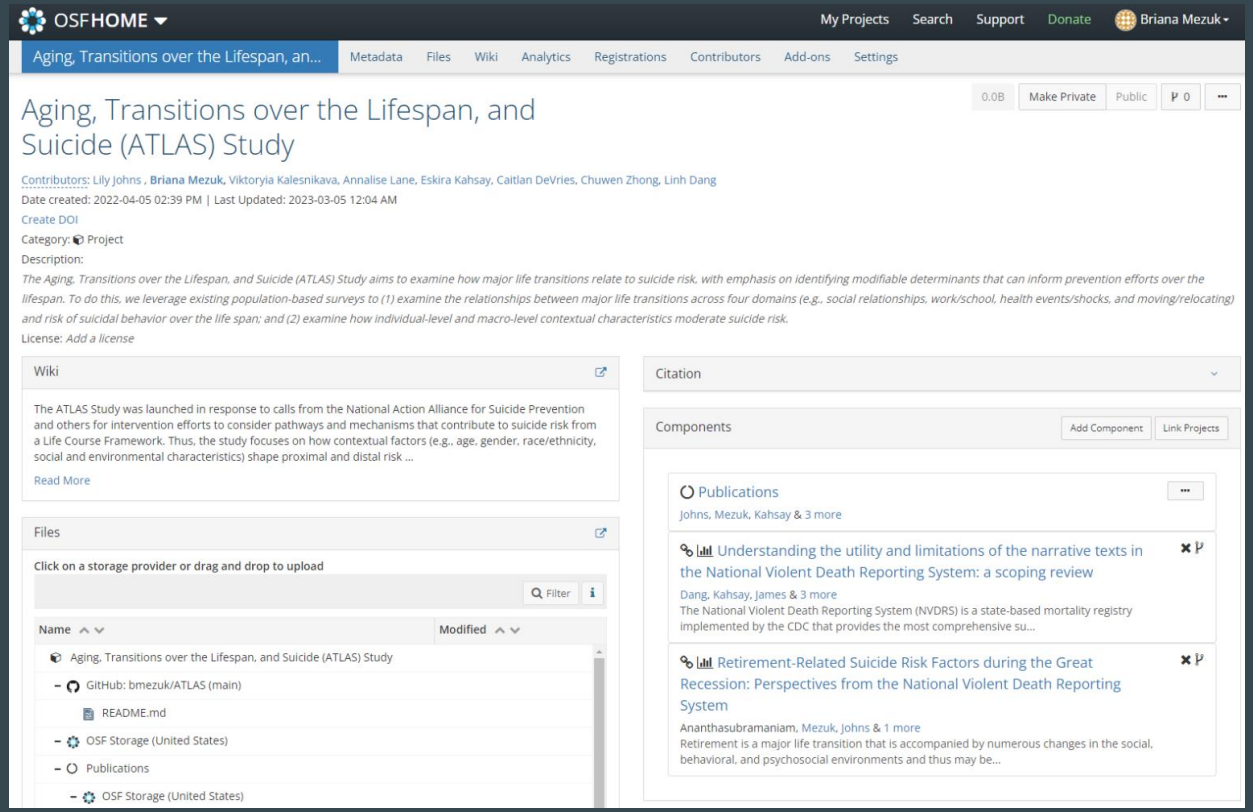
- Study rationale
  - Summary of the problem and gap in the literature you are seeking to address
- Data collection materials (if applicable)
  - Recruitment plan, IRB approval, survey instruments, codebook, etc.
- Research questions and hypotheses
- Dataset description
  - Inclusion/exclusion criteria for the sample, URL to source of data
- Variables and their operationalizations
  - Exposures
  - Outcomes
  - Confounders
  - Moderators and mediators
- Analysis plan
  - Confirmatory hypothesis
  - Exploratory hypotheses

How to pre-register

- Template I use in my own lab for pre-registrations
- Template we use in the Depression Center Data & Design Core

- Pre-registering clinical trials instructions from NIH are here.
  - Be aware of the time frame - must have this completed within 3 weeks of enrolling first subject

Example



[Scoping review pre-registration]

How much exploratory data analysis is permissible before you pre-register?

- You will need to know things like analytic sample size, how variables will be operationalized, etc. in order to complete the pre-registration itself
  - EDA to identify analytic sample size, initial data visualizations (histograms), bivariate correlations, identifying any major missing data issues, etc. are fine (and necessary!) to do before pre-registrering
- What you should not do is generate p-values (t-tests, etc) of relationships that you are seeking to test in your study

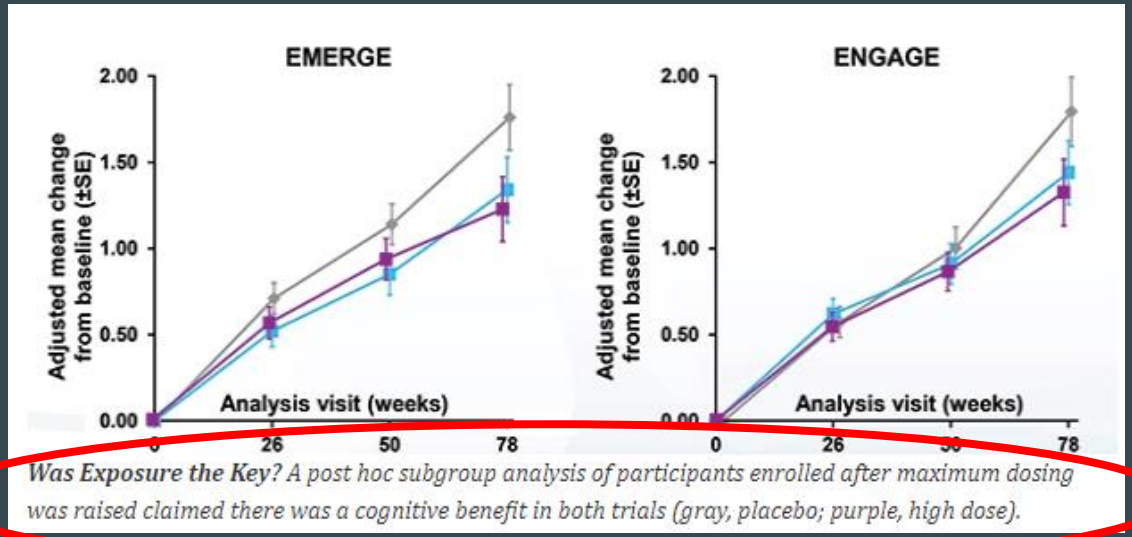
What if I did some analyses that I didn't pre-register? Can I still present them in my paper?

- Anticipate this may happen - and flag these - in the "follow-up analyses" section of your pre-registration plan so you are transparent about the "If I find X, I will pursue Y..." rabbit hole that you may go down.

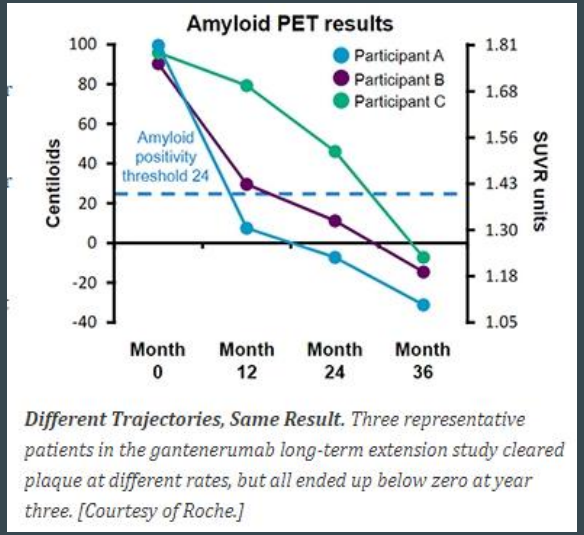
- Make it explicitly clear in your manuscript that you conducted follow-up analyses that were not pre-registered, and potentially present them in the "exploratory" manner that they are (i.e., do not present p-values but instead focus on effect sizes, like we do for pilot studies)

Controversy regarding FDA approval for Aduhelm

- June 2021: Biogen receives accelerated FDA approval for Aduhelm, the first potential "disease-modifying treatment" for mild AD
- Why was it approved? Because in Phase 3 trials (ENGAGE and EMERGE, which were halted early in 2019) to **reduce beta-amyloid...**



Was Exposure the Key? *A post hoc subgroup analysis of participants enrolled after maximum dosing was raised claimed there was a cognitive benefit in both trials (gray, placebo; purple, high dose).*



Different Trajectories, Same Result. *Three representative patients in the gantenerumab long-term extension study cleared plaque at different rates, but all ended up below zero at year three. [Courtesy of Roche.]*

Phase 3 Clinical trial protocol

Outcome Measures Go to

Primary Outcome Measures :

1. Change From Baseline in Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB) Score at Week 78 [Time Frame: Baseline, Week 78]

   CDR-SB integrates assessments from 3 domains of cognition (memory, orientation, judgment/problem-solving) and 3 domains of function (community affairs, home/hobbies, personal care). Following caregiver interview and systematic patient examination, the rater assigns a score describing the participant's current performance level in each of these domains of life functioning. Prespecified severity anchors range from none = 0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3 (the personal care domain omits the 0.5 score). "Sum of boxes" scoring methodology sums the score for each of the 6 domains and provides a value ranging from 0 to 18 that can change in increments of 0.5 or greater. Higher scores indicate greater disease severity. Mixed model for repeated measures (MMRM) analysis was used to analyze change from baseline in CDR-SB. A positive change from baseline indicates clinical decline.

… but all primary (and secondary!) pre-registered outcomes were cognitive functioning…

…which showed no difference.

Phase 3 Clinical trial protocol

In addition:

Trial recruitment was stopped early because a futility analysis showed that the drug/treatment was unlikely to beat placebo on the primary outcome.

ClinicalTrials.gov Identifier: NCT02484547

Recruitment Status : Terminated (Study was discontinued based on futility analysis done and not based on safety concerns. Follow-up visits and closing out study activities are completed)
First Posted : June 29, 2015
Results First Posted : September 2, 2021
Last Update Posted : September 2, 2021

(which was correct)

Current Phase 4 trial in Clinical Trials.gov

Primary Outcome Measures : Change From Baseline in CDR-SB Score at Week 78

Secondary outcomes:

- Change From Baseline in Integrated Alzheimer's Disease Rating Scale (iADRS) Score at Weeks 78 and 106
- Change From Baseline in ADCS-ADL-MCI Score at Weeks 78 and 106
- Change From Baseline in ADAS-Cog13 Score at Weeks 78 and 106
- Change From Baseline in Mini-Mental State Examination (MMSE) Score at Weeks 78 and 106
- Change From Baseline in Neuropsychiatric Inventory-10 (NPI-10) Score at Weeks 78 and 106
- Change From Baseline in Amyloid Positron Emission Tomography (PET) Signal at Weeks 78 and 104
- Change From Baseline in Tau PET Signal at Weeks 78 and 104
- Change From Baseline in CDR-SB Score at Week 106
- Change From Baseline in Global Statistical Test (GST) Composite Z-Score

The New York Times https://www.nytimes.com/2021/06/07/health/aduhelm-fda-alzheimers-drug.html

F.D.A. Approves Alzheimer's Drug Despite Fierce Debate Over Whether It Works

Aducanumab, or Aduhelm, is the first new Alzheimer's treatment in 18 years and the first to attack the disease process. But some experts say there's not enough evidence it can address cognitive symptoms.

By Pam Belluck and Rebecca Robbins

Published June 7, 2021 Updated July 20, 2021 7 MIN READ

The Food and Drug Administration on Monday approved the first new medication for Alzheimer's disease in nearly two decades, a contentious decision made despite opposition from the agency's independent advisory committee and some Alzheimer's experts who said there was not enough evidence that the drug can help patients.

The drug, aducanumab, which will go by the brand name Aduhelm, is a monthly intravenous infusion intended to slow cognitive decline in people with mild memory and thinking problems. It is the first approved treatment to attack the disease process of Alzheimer's instead of just addressing dementia symptoms.

Biogen, its manufacturer, announced Monday afternoon that the list price would be $56,000 a year. In addition, there will most likely be tens of thousands of dollars in costs for diagnostic testing and brain imaging.

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Further reading

"According to an article in the upcoming issue of 'The New England Journal of Medicine,' all your fears are well founded."

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Pre-registration: Weighing costs and benefits for researchers☆

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ABSTRACT

In the past decade, the social and behavioral sciences underwent a methodological revolution, offering practical prescriptions for improving the replicability and reproducibility of research results. One key to reforming science is a simple and scalable practice: pre-registration. Pre-registration constitutes pre-specifying an analysis plan prior to data collection. A growing chorus of articles discusses the prescriptive, field-wide benefits of pre-registration. To increase adoption, however, scientists need to know who currently pre-registers and understand perceived barriers to doing so. Thus, we weigh costs and benefits of pre-registration. Our survey of researchers reveals generational differences in who pre-registers and uncertainty regarding how pre-registration benefits individual researchers. We leverage these data to directly address researchers' uncertainty by clarifying why pre-registration improves the research process itself. Finally, we discuss how to pre-register and compare available resources. The present work examines the *who, why,* and *how* of pre-registration in order to weigh the costs and benefits of pre-registration to researchers and motivate continued adoption.