

What is a Data & Safety Monitoring Committee?

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IMPACT Collaboratory Annual Meeting Bethesda, MD April 6, 2022



I received research funding from Pfizer through the University of Pennsylvania, ending May 2020.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Rema Raman, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Feng He, M.S., Xiaoying Sun, M.S., Ronald G. Thomas, Ph.D., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Gopalan Sethuraman, Ph.D., and Richard Mohs, Ph.D., for the Semagacestat Study Group

NEJM 370:311, 2014





We conducted a double-blind, placebo-controlled trial in which 1537 patients with probable Alzheimer's disease underwent randomization to receive 100 mg of semagacestat, 140 mg of semagacestat, or placebo daily. Changes in cognition from baseline to week 76 were assessed with the use of the cognitive subscale of the Alzheimer's Disease Assessment Scale for cognition (ADAS-cog), on which scores range from 0 to 70 and higher scores indicate greater cognitive impairment, and changes in functioning were assessed with the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale, on which scores range from 0 to 78 and higher scores indicate better functioning. A mixed-model repeated-measures analysis was used.



What did the investigators of the semagacestat trial need to monitor as the trial proceeded?

- Accrual
- Data quality
- Fidelity to protocol
- Safety
- Efficacy
 - Futility
 - Early, convincing evidence of benefit



How might they have chosen to monitor these items?

- Sponsor or investigator
- Independent individual ("safety monitor")
- Independent group
 - "Data & safety monitoring board (DSMB)"
 - "(Independent) data monitoring committee (I/DMC)"



Problems with monitoring by sponsor or investigator

- Bias and vested interests
- Temptation to alter study design or conduct based on interim data
- For some analyses, need to unmask data/do between-group comparisons
- Ability to maintain confidentiality of data & interim analyses
- May threaten ability to continue trial



Problems with monitoring by independent individual

Monitoring is complex & requires diverse disciplinary expertise

- Clinical
- Biostatistical
- ?Ethics



NIA requirements for data & safety monitoring

| NIH National Institute on Aging | | | | | | | |
|--|---|---------------|--|--|--|--|--|
| COVID-19 | | | | | | | |
| Get the latest public health information from CDC » Get the latest research information from NIH Español » NIH staff guida | | | | | | | |
| HEALTH INFORMATION | RESEARCH & FUNDING | NEWS & EVENTS | | | | | |
| Home / Research & Funding / Grants & Funding / NIA Guidance On Clinical Trials | | | | | | | |
| NIA-SPECIFIC FUNDING POLICIES | NIA Guidance on Clinical Trials | | | | | | |
| NIH FUNDING POLICIES | Introduction Data and Safety Monitoring | | | | | | |
| RESEARCH GRANT | Studies with a DSMB | | | | | | |
| MECHANISMS | DSMB Process, Role and Responsibilities | | | | | | |
| THE PROCESS OF GETTING | DSMB Meetings – Research Grants | | | | | | |
| AN NIH GRANT | DSMB Meetings – Cooperative Agreements | | | | | | |
| INSIDE NIA: A BLOG FOR | • Inquiries | | | | | | |

https://www.nia.nih.gov/research/grants-funding/nia-guidance-clinical-trials See also: https://grants.nih.gov/grants/guide/notice-files/not98-084.html

Data and Safety Monitoring

Guidance for Investigators

Applicants requesting support for any intervention study must complete "PHS Human Subjects and Clinical Trials Information" form of the SF424 (R&R), describe a data and safety monitoring plan (DSMP), which discusses the need for an independent data and safety monitoring body or justifies why such a body is not needed to monitor the study and proposes an alternative safety monitoring mechanism. For example, for a single-site, low risk study, the PI may propose a local safety monitor, instead of a DSMB.

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When is a DSMB needed?

- Two or more of:
 - Trial intended to provide definitive info about efficacy &/or safety of medical intervention
 - Intervention may have significant toxicity
 - Trial evaluates mortality or other major endpoint
 - Trial should stop early if primary question has been definitively answered
- My addition: monitoring by sponsor would create unacceptable risk of bias or threaten completion of trial

Data Monitoring Committees in Clinical Trials. Hoboken: Wiley, 2019



What does a DSMB review (1)?

Study integrity & quality

- Accrual (including by strata, subgroup, etc)
- Data quality (missing data, case report form completion, etc.) sometimes by arm



What does a DSMB review (2)?

Safety

- Individual (serious/unexpected) safety events
- Aggregate safety events, by arm

- If serious concerns, can recommend modifying procedures, modifying consent, pausing trial, dropping arm, permanently terminating trial



What does a DSMB review (3)?

- Efficacy (at prespecified intervals)
 - Futility
 - very unlikely that trial will show difference in favor of novel therapy
 - Benefit
 - Interim data show convincingly that novel therapy is better than control
- <u>Guided</u> by prespecified "stopping rules"



How does a DSMB meeting proceed?

- Open meeting (DSMB, investigators/sponsor)
- Closed meeting (DSMB, unmasked statistician ± safety monitor)
- Closed executive session (DSMB only)
- Written ± verbal report to investigator/sponsor
 - Recommendations are advisory



What happened in the semagacestat trial?

DSMB recommended early stopping due to futility

Table 2. Estimated Mean Change from Baseline for the Coprimary and Secondary Outcomes, According to a Mixed-Model Repeated-Measures Analysis.*

| Outcome | Placebo | Semagacestat, 100 mg | Semagacestat, 140 mg | P Values | |
|---|------------------------|-------------------------|-------------------------|--|--|
| | | | | Sema- gacestat, 100 mg, vs. Placebo | Sema- gacestat, 140 mg, vs. Placebo |
| ADAS-cog score | | | | 0.15 | 0.07 |
| No. of participants with results | 486 | 483 | 497 | | |
| M <mark>ean change in score (95% CI)</mark> | 6.4 (5.48 to 7.40) | 7.5 (6.44 to 8.53) | 7.8 (6.72 to 8.85) | | |
| ADCS–ADL† | | | | 0.14 | < 0.001 |
| No. of participants with results | 480 | 481 | 490 | | |
| Mean change in score (95% CI) | –9.0 (–10.37 to –7.67) | –10.5 (–11.94 to –9.07) | -12.6 (-14.1 to -11.2) | | |



Bottom line: for high-stakes trials, DSMBs are essential to both human subjects protection & trial integrity

- Ensure high-quality conduct
- Protect safety of trial participants
- Ensure confidentiality of interim data
- Make unbiased, expert recommendations about early stopping due to futility, safety, or convincing evidence of efficacy





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Data Monitoring for PCTs

Stephanie Morain, PhD, MPH

Assistant Professor Berman Institute of Bioethics Dept Health Policy & Management, Johns Hopkins Bloomberg School of Public Health





IMPACT Collaboratory Annual Meeting Bethesda, MD April 6, 2022

Key Takeaway:

"Pragmatic" nature of PCTs can present distinct considerations for data monitoring

... and these considerations can be managed prospectively



Roadmap:

- 1. Why monitoring in PCTs "different"
- 2. Suggestions for DSMBs & investigators
- 3. Resources for further guidance



Data Monitoring Considerations for PCTs (1)

Adherence & Fidelity: Should we monitor for adherence?

- Monitoring inconsistent with "pragmatic" aspect of PCT
- Failure of adherence may reflect how trial would be implemented in the real-world setting
- Adherence data needed to evaluate finding of 'no effect'



Data Monitoring Considerations for PCTs (2)

Trial Design Effects and Impact on Monitoring

- 1. Potential for different intensity of follow-up by study arm (will impact assessment of outcomes)
- 2. Impact of cluster design
 - a) Greater heterogeneity across sites in...
 - a) Patients
 - b) Intervention delivery
 - c) How/when data collected & reported
 - b) Need to account for cluster-level effects in statistical analysis



Data Monitoring Considerations for PCTs (3)

Timeliness & Availability of Data for Interim Analyses

- 1. Reliance on EHRs/extant data may influence feasibility of monitoring
 - a) Outcome data may not be available until enrollment is complete

b) Privacy considerations may mean data analyzed individually at each site, with only summary data aggregated



Data Monitoring Considerations for PCTs (4)

Early Termination Decisions

- 1. Operational Considerations
 - data (un)availability & monitoring for safety
- 2. Epistemic Considerations
 - greater pre-existing data on expected harms
- 3. Normative Considerations



Early Termination: Normative Considerations

- 1. Impact of waivers/alterations of informed consent?
- 2. How to assess whether data "sufficient" to prompt changes in practice?
- 3. Should stopping boundaries be asymmetric?
- 4. Relevance of the nature of the intervention? Availability outside the trial?
- 5. What duties are owed to patient-subjects in PCTs? Is the nature of this duty different as compared to what is owed to explanatory trial participants?



Additional Challenge for IMPACT:

1. Monitoring & consideration for direct, indirect, & collateral participants



General Recommendations

- A. Early communication between trial leadership & DSMB to develop shared understanding of goals and scope of data monitoring
- B. Ensure those charged with data monitoring have relevant expertise, including:
 - health informatics
 - operational/health system considerations
 - PCTs
 - patients/caregivers (?)



Available Resources from NIH Pragmatic Clinical Trials Collaboratory





Available Resources from NIH Pragmatic Clinical Trials Collaboratory





Available Resources from NIH Pragmatic Clinical Trials Collaboratory

Health Care Systems Research Collaboratory

Data Monitoring in Pragmatic Clinical Trials: Points to Consider TEMPLATE

DATA MONITORING COMMITTEE (DMC) CHARTER FOR PRAGMATIC CLINICAL TRIALS

TITLE OF PROTOCOL:

PROTOCOL NUMBER:

SPONSOR OF PROTOCOL:

DATE OF DOCUMENT:

• NIH Collaboratory Rethinking Clinical Trials®

Health Care Systems Research Collaboratory

Early Stopping in Pragmatic Clinical Trials: Workshop Summary





Case Studies



Case Study # 1

Kenneth Hepburn, PhD



Pragmatic Tele-Savvy: Randomized Trial of a Synchronous/Asynchronous Psychoeducation Program for Family Caregivers of Persons Living with Dementia Kenneth Hepburn, PhD

Study question:

Does the online intervention, compared to a fully asynchronous attention control condition, increase caregiver competence and reduce stress in family caregivers at two clinic settings?

Population:

Dementia Family Caregivers (N=100)

Design:

Individually randomized trial at 2 sites in the US

Outcome Data Sources:

- 1. Caregiver self-administered questionnaires identical to Tele-Savvy efficacy trial
- 2. At Connecticut site: questionnaires built into electronic health record using caregiver proxy access into patient portal



- How is the DSMB set up?
 - No DSMB; Safety Officer assigned to study based on low risk
- Are there stopping rules?
 - None
- Are there specific safety components?
 - For Tele-Savvy component: Interventionist follows an established safety protocol for observed over-stress in caregiver participants
- How are adverse events dealt with?
 - Reported by Tele-Savvy instructors to study coordinator
 - SAEs would be reported to Safety Officer per protocol
 - Largely focused on monitoring observed over-stress





Case Study # 2

Nicholas Pajewski, PhD



Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults (PREVENTABLE)

Nicholas Pajewski, PhD

Study question:

In adults 75 years or older free of CVD, does a moderate intensity statin improve survival free of dementia and persistent disability? Secondarily, does it reduce the incidence of CVD?

Population:

Ambulatory, community-dwelling older adults (N=20,000)

Design:

Individually randomized trial at ~90 sites in the US

Outcome Data Sources:

- 1. Telephone Call Center (Cognitive Screening / ADL by self-report)
- 2. Electronic Health Record (PCORnet, VA, and individual health systems)
- 3. Medicare Claims
- 4. National Death Index

www.preventabletrial.org



- How is the DSMB set up?
 - 7 members (5 MDs spanning Geriatrics/Cardiology/Neurology, 2 biostatisticians), Meets every 6 months, mixed experience on pragmatic trials
- Are there stopping rules?
 - None. Contemplated interim analyses, advice from DSMB statisticians was to drop it due to data lags
- Are there specific safety components?
 - Depressive screen as part of cognitive screening (PHQ-8), hospitalizations (EHR + claims), death
- How are adverse events dealt with?
 - Very passive ascertainment = Only annual telephone follow-up
 - FDA advice = We know what we need to know about statin AEs
 - Largely focused on monitoring deaths





Case Study # 3

Joshua Chodosh, MD, MSHS, FACP



Enhanced Quality in Primary Care for Elders with Diabetes and Dementia (EQUIPED-ADRD) Joshua Chodosh, MD, MSHS, FACP

Study question:

Will practice guidelines and a quality improvement program featuring panel managers improve patient symptoms and quality of life, decrease patient and caregiver management burden and improve care quality (desirable glycemic and blood pressure ranges) based on patient/caregiver preferences while decreasing acute care utilization

Population:

Adults 65 years or older with co-occurring diabetes and dementia in FGP and FHC seen in primary care or endocrine clinics (N=1,000)

Design:

Cluster randomization (by clinic) in 32 NYU affiliated clinics

Outcome Data Sources:

- 1. Telephone Interviews with Caregivers
- 2. Electronic Health Records
- 3. Medicare Claims

Primary Endpoint:

Number of patients who are in a desirable glycemic and blood pressure ranges

https://clinicaltrials.gov/ct2/show/NCT03723707



- How is the DSMB set up?
 - 3 members (2 MDs (geriatricians), 1 biostatistician), meet every 6 months in an open and closed session
- Are there stopping rules?
 - None
- Are there specific safety components?
 - Hyper/hypoglycemia, increased urinary symptoms, falls, syncope
- How are adverse events dealt with?
 - All electronic health record-triggered alerts from individual patients seen in the ED or admitted are reviewed by PI; attribution to the study intervention is determined and reported in the patient's EHR
 - Caregiver reported deaths that occur outside NYU Health are reviewed and reported to the patient's EHR and reviewed by the PI
 - Deaths is considered an expected (non-study-attributed) outcome in this population





Case Study # 4

Ab Brody, PhD, RN, FAAN



The Dementia Symptom Management at Home (DSM-H) Trial Ab Brody, PhD, RN, FAAN

Study question:

Does a multi-component QI intervention targeted at skilled home health care teams improve outcomes for PLWD and their Care Partners?

Population:

PLWD newly admitted to skilled home health care who have a primary care partner and live in a private residence

Design:

Cluster Randomized trial in 20 care teams at 3 home health agencies

Primary endpoint:

Quality of Life for both the PLWD and Care partner

https://doi.org/10.1016/j.cct.2020.106005



- How is the DSMB set up?
 - 3 Person (MD, Nurse Researcher, Statistician), Meets every 6 months, all have worked on pragmatic trials
- Are there stopping rules?
 - No Pre-defined Stopping Rules (originally included and DSMB asked they be removed
- Are there specific safety components?
 - DSMB required a delirium screen of PLWD
 - PHQ-9 for care partners, and each + Suicidal Ideation needs to be assessed
- How are adverse events dealt with?
 - Individually included in report, only SAE directly related to intervention or unexpected must be immediately reported
 - Death is considered an expected outcome in this population





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