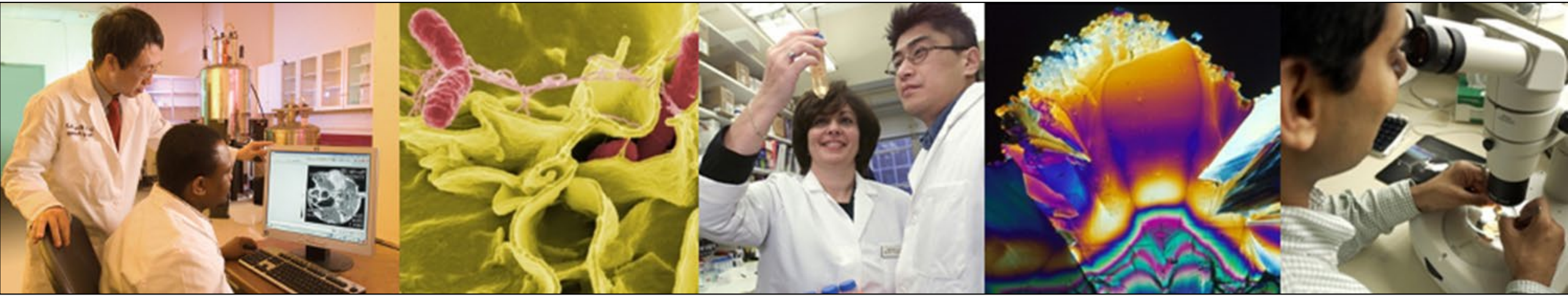
NIH Response to ACD Moderate Alcohol and Cardiovascular Health (MACH) Trial Review and Recommendations

117th Meeting of the Advisory Committee to the Director
December 13, 2018



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Background

- The Moderate Alcohol and Cardiovascular Health (MACH) trial was a multicenter, randomized clinical trial designed to determine the effects of one serving of alcohol daily (compared to no alcohol intake) on the rate of new cases of cardiovascular disease and the rate of new cases of diabetes among participants free of diabetes at baseline.
- The trial was funded in part by the National Institute of Alcohol Abuse and Alcoholism (NIAAA), and in part through private donations to the Foundation for the National Institutes of Health (FNIH).
- Prompted by concerns raised by current NIH and FNIH leadership, and a March 2018 report in the media, the Director of NIH requested reviews of the Moderate Alcohol and Cardiovascular Health (MACH) trial.

Background (cont.)

- The ACD working group reviewed the scientific premise of and the planning for the trial, processes used to support the trial, and the NIAAA research portfolio. The working group report stated that:
  - NIAAA staff members' early and frequent engagement with industry representatives calls into question the impartiality of the process by which the study was planned
  - NIAAA staff members' sustained interactions with the eventual lead investigator of the MACH trial provided this scientist with a competitive advantage not available to other applicants, effectively steering funding to a pre-selected investigator

Background (cont.)

- The ACD working group reviewed the scientific premise of and the planning for the trial, processes used to support the trial, and the NIAAA research portfolio. The working group report stated that:
  - These issues, in combination with concerns about a study design that may not be powered appropriately to detect adverse outcomes, undermine the study and cast doubt on whether the scientific knowledge gained from the study would be credible

Summary of June 2018 Recommendations Accepted by the NIH Director

- Support the NIH Director's decision to suspend the MACH trial
- Recommend that the MACH trial be terminated
- The NIH should examine additional measures to prevent NIH staff from soliciting external funding to support programs
- NIH Institutes, Centers, and Offices (ICOs) should ensure that program staff do not inappropriately provide non-public information, or engage in deliberations that either give the appearance of, or provide, an advantage to any single, or subset of, investigator(s)

Summary of June 2018 Recommendations Accepted by the NIH Director (cont.)

- The NIH should examine additional measures to assiduously avoid providing, or giving the appearance of providing, an advantage to any single, or subset of, investigator(s) (for example, in guiding the scientific substance of preparing grant applications or responding to reviewer comments)
- The NIH should ensure that ICOs are uniformly applying IC policies, procedures, and processes for vetting possible FOAs and presenting those possible FOAs to specific bodies (for example, Board of External Experts or National Advisory Council)

This Represents a Critical Moment

- Issues highlighted by the MACH trial review threaten public trust
- To maintain public trust in NIH we require processes that support:
  - Transparency
  - Impartiality
  - Research Integrity

NIH Responses to the June 2018 ACD Recommendations

- We have engaged leadership and staff across NIH to:
  - Develop parameters for review and to identify best practices
    - NIH engagement with outside (industry, non-profit) partners (Including) vetting process used by NIH to enter into NIH-FNIH partnerships
    - NIH engagement with extramural community
      - program officer roles & responsibilities
      - funding opportunity development
  - Begin a systematic examination of existing projects and processes to identify concerns and potential areas of improvement raised by the MACH trial review

Engagement with Outside Partners – General Principles

- Reviews of all PPPs must integrate a contextual assessment of reputational risk to the agency
- Final decisions on trial design and data analysis approaches must be made by NIH
- Additional measures – including identification of transparency standards & best practices – will improve stewardship

Engagement with Outside Partners – General Principles, continued

- When evaluating potential donations from an organization or industry, basic considerations for NIH's risk analysis (including reputational risk) should include:
  - the mission of the donor
  - the magnitude of the gift
  - whether the gift is conditional/unconditional
  - "quid pro quo" expectations (or the potential for such expectations)

Rationale for Industry Involvement: Selective Examples

- Partnerships with industry for clinical trials
  - Need products to conduct the trial
  - Approach industry about conducting a trial due to scientific or public health need
  - Receive advice on protocols from industry, although final decisions made by the IC

NIH-FNIH *Request for Collaboration* Form and Vetting Process

While the ACD Working Group review and NIH review did not find any issues with the FNIH MOU in the case of MACH, NIH is taking steps to improve this process, including:

- Adding greater specificity to the steering committee charge
- Identifying additional questions to ask on RFC form to document interactions leading up to the RFC process
  - frequency of interactions, type of interactions, etc.
- Determining the need for:
  - increased awareness of FNIH RFC process and best practices
  - enhanced COI protocols and disclosure policies

Centralized Reporting of “Declined Partners”

- NIH will track circumstances where a partnership with an outside organization is declined for a non-scientific reason to mitigate partner “shopping” among ICOs

Comprehensive and Systematic Review
Part I: Engagement with Outside Partners

- Informed by the principles identified, and guided by a standard, centrally defined process, all ICO directors will be responsible for
  - systematically assessing both their current and future public-private partnerships to ensure that they meet all standards, rules, and regulations

Points of Consideration
Part I: Engagement with Outside Partners

- For partnerships with industry or non-profits over the past 24 months
  - Documentation of process used to select outside organization, including consideration of potential reputational risk, and the nature of interactions of staff with outside organization leading up to selection
  - Assurance that FOA(s) supported, in part, by outside organization were publicly cleared
  - Clear definition of what asset(s) are being obtained from outside organization and what restrictions/risks they may entail

Engagement with Extramural Community – General Principles

- Program officer roles & responsibilities
  - Core values for program officers are framed across 4 dimensions, with program officials working as:
    - scientists
    - administrators
    - communicators
    - stewards
- It is paramount that NIH promote a culture of impartiality and responsibility within the program community regarding acceptable levels of interaction
- POs should not be advocates of specific **scientists** – emphasis should be placed on identifying scientific program needs that benefit the IC mission

Engagement with Extramural Community – General Principles, continued

- Funding opportunities need to support fair and open competition
  - Recall: in the situation of MACH, there was extensive engagement with 2-3 PIs who provided input into the structure and content of the FOA as it was being written. In addition, the FOA was not presented in an open council session.

- All concept clearance of FOAs (e.g., RFAs, PARs) must be done at an open Council session (or similar public external advisory session)
  - The concept clearance presentation must address the outcomes of any workshop proceedings which informed the FOA development
  - Extramural scientists, including those who have attended a workshop, should NOT play a direct role in writing FOAs

Workshop Transparency

To address the fundamental principle of transparency, all NIH workshops that are held specifically to inform potential development of funding opportunity announcements must be publicly accessible electronically

This could take the form of one of the following:

- Real-time webcast (preferably interactive)
- Post-meeting video made available in a short time frame after the meeting and well in advance of any FOA publication.
- Written meeting documentation:
  - Full transcript
  - A minimally acceptable standard: full disclosure of participants; slide presentations; meeting summary

Meeting materials should be posted within 6 weeks after the meeting, or 30 days prior to publication of FOA

Comprehensive and Systematic Review – Part II

- Informed by the principles identified, and guided by a standard, centrally defined process, all ICO directors will be responsible for
  - systematically assessing both their current and future public-private partnerships to ensure that they meet all standards, rules, and regulations

- ICO directors will also be responsible for ensuring that their program staff engage extramural investigators in an impartial manner that is fair to all

Points of Consideration in Comprehensive and Systematic Review – Part II

- For extramural staff engagement
  - Adoption of NIH-wide standards for explicit roles and responsibilities for Program Officers to ensure that program staff interactions with community maintain impartiality with no favored treatment for any investigator
- For funding opportunity announcements
  - Concept clearances for all FOAs to be discussed in a public/open session
  - Workshops informing FOA development should where practical be open via interactive webinar or videocast
    - When it is not possible to hold a webinar or videocast, a full transcript, or as a minimally acceptable standard: full disclosure of participants, and all slide presentations and a meeting summary will be posted within 6 weeks after the meeting, or 30 days prior to publication of FOA

Acknowledgements

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Discussion