NIH Report to the Advisory Committee to the Director (ACD)

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

DECEMBER 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. Two concurrent reviews took place, one by the NIH Office of Management Assessment, and the other by a working group of the NIH Advisory Committee to the Director (ACD). The ACD working group was charged to review the scientific premise of and planning for the MACH trial; the process used to decide the support of the MACH trial; the program development and oversight once funding was secured by the FNIH; and, a review of the NIAAA research portfolio prior to and under during the leadership of the current NIAAA director.

The working group report, presented at the June 2018 meeting of the ACD, stated that:

- NIAAA staff members' early and frequent engagement with representatives of the alcohol industry (many of whom worked at companies that later made donations to support the study) 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.
- 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. [1]

ACD Recommendations & Further Review Requested

The working group recommendations, accepted by the ACD and the NIH Director in June 2018, were that NIH:

- Not continue the trial, given:
    - early and frequent industry interactions to gain support for the study
    - irregularities in funding opportunity design

[1] NIH Advisory Committee to the Director, "ACD Working Group for Review of the Moderate Alcohol and Cardiovascular Health Trial," June 2018; NIH Advisory Committee to the Director (ACD), "Report of the ACD Working Group for Review of the Moderate Alcohol and Cardiovascular Health Trial," June 2018.

    - actions and emails by members of NIAAA senior staff that communicate their intent to avoid open competition for research funding
    - actions by members of NIAAA senior staff indicating the intent to effectively preselect the principal investigator of the MACH trial
    - concerns about study design

- Examine additional steps to prevent NIH staff attempts to solicit external co-funding to support extramural research programs across NIH
- Examine what measures could identify potential industry influence or irregularities in funding opportunity design
- Examine what measures could identify potentially inappropriate engagement with principal investigators to influence funding opportunity announcement development and funding outcomes
- Examine how Institutes, Centers, and Offices (ICOs) can 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)
- 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)
- Examine additional measures to assiduously avoid giving the appearance of, or providing, an advantage (for example, in guiding the scientific substance of preparing grant applications or responding to reviewer comments) to any single, or subset of, investigator(s)
- Include additional questions at time of Request for Collaboration filing, to identify NIH staff interactions/pre-engagement with donors, and the process by which the filer has identified "potential donors" in the form

At the June 2018 meeting, in addition to accepting the ACD's recommendations, the NIH Director charged NIH leadership to identify issues related to the MACH trial and additional areas of concern, for a thorough review of NIH's portfolio.

NIH Responses to the June 2018 ACD Recommendations

Closeout of MACH Trial

The NIH Office of Extramural Research and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) worked with the grantee institution on an orderly closeout to the trial. The closeout is underway and will end formally on January 31, 2019.

Follow-up Activities

NIH engaged leadership across its 27 ICs and the Office of the Director to follow up on the ACD recommendations. To develop additional measures to strengthen NIH processes for

establishing public-private partnerships and program development processes, and in order to perform a detailed review of existing projects for similar cases, NIH's first steps were to identify both the areas of concern, and the junctures for process improvement, as brought to light by the MACH trial.

NIH leadership identified several areas of focus, including:

- The NIH-FNIH Request for Collaboration form and vetting process
- Engagement of staff with industry partners
- Extramural community engagement
    - funding opportunity development
    - program officer roles & responsibilities

Principles & Activities Related to Key Areas

NIH-FNIH Request for Collaboration 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 identified steps to improve the Request for Collaboration application and review process. These include:

- Revising the charge to the FNIH-NIH Steering Committee: Adding greater specificity to the charge will make clear what the committee needs to review and consider in making their decisions.

- Identifying additional questions to ask on the RFC form: While the form already asks about whether potential donors have been identified, additional questions will be added to more specifically ask about interactions leading up to the RFC process, such as frequency of interactions, type of communications/meetings, etc.

- Increased awareness of FNIH RFC process and best practices among NIH staff: To ensure that NIH staff understand the FNIH process, NIH will determine the need for enhanced communication about this process with NIH staff.

- Identifying improvements for conflict of interest protocols and disclosure policies for clinical trials: A recent JAMA editorial [2] notes that the MACH trial's record on ClinicalTrials.gov did not identify financial support through the FNIH. They describe that funding from 5 alcohol manufacturers is mentioned on the Foundation for the NIH

[2] Bernard Lo and Deborah Grady, "Protecting NIH's Integrity and Trustworthiness in Public-Private Partnerships," *JAMA* 320, no. 5 (August 7, 2018): 439–40, https://doi.org/10.1001/jama.2018.7625.

website, but not on the MACH website or on the trial registry at ClinicalTrials.gov, where only the NIAAA is named as the sponsor.

At the time of this report, NIH has already drafted a revised steering committee charge, revised criteria for evaluation of Requests for Collaboration, and added questions to the Request for Collaboration form for a greater level of specificity in documenting interactions with potential donors. These draft materials are included in the appendix.

Engagement of staff with industry partners

The MACH trial scenario specifically involved soliciting financial support from the alcohol industry to the NIH, and this financial support would then be used to support a specific extramural research project. However, to address crucial scientific or public health needs, NIH staff also seek support from industry scientists in the form of different equities (e.g., scientific expertise, in-kind donations of unique equities such as small molecule, biological, device). Partnerships with industry for clinical trials may be due to: needing products to conduct the trial, approaching industry to conduct a trial or to increase industry interest in developing interventions based on the scientific or public health needs identified by NIH, or receiving advice on protocols from industry scientists (with final decisions about the research design made by NIH staff).

NIH identified a number of key principles that will enhance stewardship of industry partnerships, and non-profit partnerships as well, when appropriate.

These include:

1) Final decisions on trial design and data analysis approaches must be made by NIH**.**
2) Identification of transparency standards & best practices will improve stewardship of public-private partnerships.
3) Reviews of public-private partnerships should integrate a contextual assessment of reputational risk to the agency.
4) When evaluating potential donations from an organization or industry, basic considerations for the agency's risk analysis (including reputational risk) should include:

- the mission of the partner
- the magnitude of the gift
- whether the gift is restricted/unrestricted
- 'quid pro quo' expectations (or the potential for such expectations)

NIH will also review best practices identified by, for example, the Centers for Disease Control and Prevention (CDC) Ethical Considerations for Public-Private Partnerships workgroup [3], to identify additional transparency opportunities that may be applicable to NIH business models as well.

[3] CDC ACD Working Group, "Ethical Considerations for Public-Private Partnerships," 2016.

NIH will also begin to centrally track circumstances where an NIH Insititute, Center, or Office (ICO) declines a partnership with an outside organization non-scientific reasons (e.g., reputational concern). Sharing this information across NIH will mitigate risks of an external partner potentially "shopping" among ICOs.

Extramural community engagement —–funding opportunity development

During the program development and planning which preceded the funding of the MACH trial, there was extensive engagement with 2-3 principal investigators (PIs) who provided input into the structure and content of the funding opportunity announcement (FOA) as it was being written. These PIs were the eventual project leads of the MACH trial. In addition, the FOA was not presented in an open council session, further conferring an advantage to the PIs who had frequent interactions with NIAAA staff members writing the FOA.

Funding opportunities need to support fair and open competition. NIH identified a number of recommendations to enhance transparency into the funding opportunity announcement development process. These include:

1) Clearance of FOAs should be done at an open Council session (or similar public external advisory session). The concept clearance presentation should address the outcomes of any workshop proceedings which informed the FOA's development.

2) Extramural scientists, including those who have attended a workshop, should **not** play a direct role in writing FOAs.

3) To address the fundamental principle of transparency, all NIH workshops that are held specifically to inform potential development of funding opportunity announcements should be publicly accessible electronically. This could take the form of a:

- Real-time webcast (preferred option, and preferably with an interactive setup);
- Post-meeting video;
- Written meeting documentation, such as a full transcript, or, as a minimally acceptable standard: disclosure of participants; slide presentations; meeting summary.

Workshop meeting materials, as described above, should be posted within 6 weeks after the meeting, or 30 days prior to the publication of the resultant FOA.

Extramural community engagement —–program officer roles & responsibilities

In the program development of the MACH trial, NIAAA staff members' sustained interactions with the eventual lead investigator of the MACH trial provided a single scientist with a competitive advantage not available to other applicants, effectively steering funding to a pre-selected investigator. NIH identified a number of general principles and actions to enhance understanding of staff (program officer) roles and responsibilities.

General principles include:

1) Core values for program officers have multiple dimensions 4 dimensions, with program officials working as:

- scientists
- administrators
- communicators
- stewards

2) It is paramount that NIH promote a culture of impartiality and responsibility within the program community regarding acceptable levels of interaction.

3) Program officers should not be advocates of specific **scientists** – emphasis should be placed on identifying scientific program needs that benefit the IC mission.

Actions NIH will pursue, informed by the core values aforementioned, include:

1) Clarifying program staff roles
2) Identifying whether staff policy revisions or updates are needed
3) Creating additional training materials for use across NIH
4) Additional training and educational opportunities for staff, as needed

Comprehensive and systematic review

In addition to engaging leadership to identify the issues with the MACH trial, we have likewise developed parameters for a systematic examination of existing projects and processes.

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.

For partnerships with industry or non-profits over the past 24 months, we will identify:

- Documentation of processes 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
- Assurances that FOA(s) supported, in part, by outside organization were publicly cleared
- Clear definitions of what asset(s) are being obtained from outside organization and what restrictions/risks they may entail

In addition, ICO directors will also be responsible for ensuring that their program staff engage extramural investigators in an impartial manner that is fair to all. We will adopt 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. We will likewise adopt enhanced NIH-wide standards for concept clearances of

FOAs, and workshop transparency. Concept clearances for all FOAs will be discussed in a public/open session, and workshops informing FOA development should -- where practical -- be open to all via an interactive webinar or videocast. When it is not possible to hold a webinar or videocast, a full transcript can be posted. A minimally acceptable standard would be full disclosure of participants, and all slide presentations and a meeting summary posted within 6 weeks after the meeting, or 30 days prior to the publication of an FOA.

Awareness and engagement of stakeholders

Our approach in response to the ACD recommendations has involved many stakeholders across NIH for input, including NIH IC leadership, and senior extramural program leaders.

This report *highlights* our areas of activity and actions thus far. Additional comprehensive review activities will continue to take place beyond the publication of this report and its presentation at the December 2018 ACD meeting.

A key activity is raising awareness across all NIH staff roles that may intersect with the issues raised by the MACH review. Our work will also include continued community engagement on these issues with stakeholder groups at NIH, and with the external stakeholders of NIH-supported biomedical research.

References

NIH Advisory Committee to the Director. "ACD Working Group for Review of the Moderate Alcohol and Cardiovascular Health Trial," June 2018.

CDC ACD Working Group. "Ethical Considerations for Public-Private Partnerships," 2016.

Lo, Bernard, and Deborah Grady. "Protecting NIH's Integrity and Trustworthiness in Public-Private Partnerships." *JAMA* 320, no. 5 (August 7, 2018): 439–40. https://doi.org/10.1001/jama.2018.7625.

NIH Advisory Committee to the Director (ACD). "Report of the ACD Working Group for Review of the Moderate Alcohol and Cardiovascular Health Trial," June 2018.

Appendix

FNIH-NIH Collaboration or Partnership Criteria

Project Title:

Evaluation Criteria	OSP Score (1/0)	OSP Rationale	SC Score (1/0)	SC Rationale and/or Comments
1. The collaboration or partnership is consistent with NIH's mission and goals.				
2. The IC Director, by signing the RFC, assures that the project is a priority of the IC and that appropriate procedures were followed in engaging potential partners.				
3. The collaboration or partnership does not involve an organization that has a mission contrary in purpose to NIH or the U.S. government.				
4. The collaboration or partnership does not consist of work currently being conducted by the IC or NIH (not duplicative) and/or meets an unaddressed need. If the proposed work overlaps with or resembles current efforts, the unique aspect of this project is clearly defined.				
5. The collaboration or partnership is well defined, with milestones and a timeline for completion.				
6. The expected outcomes and benefits of the partnership are explicitly defined.				

7. The budget for the collaboration or partnership clearly defines NIH and partner contributions.				
8. The collaboration or partnership leverages resources across multiple sectors with synergistic effect.				
9. Partnering with the potential private entity or entities does not present a real or perceived conflict of interest for the NIH or the IC has proposed adequate management of real or perceived conflicts.				
10. Where possible, the partnership will have appropriate transparency measures in place (e.g., website for activity, publicly available governance structure information, conflict of interest policies).				
Total:				

Form updated October 2018
IC Submission Date:
OSP Review Date:

REQUEST FOR COLLABORATION
PUBLIC PRIVATE PARTNERSHIP

SUBMISSION FORM

When complete, send to elizabeth.baden@nih.gov

A. General Information

1. Submission Date:

B. Contact Information

2. Primary NIH IC:

3. Other ICs or government agencies already involved in this project:

4. Main IC contact for this Collaboration:

   - Name:
   - Title:
   - Email:
   - Phone Number:

5. IC Director Signature: _____

   By signing this Request for Collaboration, the signee assures that the project is a priority for the IC and that, to the extent possible, appropriate procedures were followed in engaging potential partners.

C. About the Project

6. What is the name of the project?

7. Briefly describe the nature of the project. What are the purpose, scope, and goals of your project? What will the project do, who will do what, what results are anticipated? In what context will the results be useful?

8. Describe the project timeline, deliverables and milestones.

9. How does this project fit within NIH's mission and goals? How will this project advance the scientific field?

10. What critical needs is your project addressing?

11. Are there other projects (or products) underway in the scientific community (both internal and external to NIH) that you are aware of with similar or related objectives?

12. Describe the potential public health benefit of the project.

13. Describe the past activities and progress to date for the proposed project, including initial meetings, established collaborations or committees, and grants/contracts funded.

14. Does this project include any meetings, conferences or symposia?

D. Role of the NIH IC

15. What are some of the key scientific and/or administrative roles of the NIH IC (e.g., expertise, grant review and administration, access to samples, running clinical trials, providing funding)?

16. Are there anticipated funding/grant awards? When do you expect that the RFA(s) will be published and the award(s) made?

E. Role of the FNIH (Examples of FNIH activities are listed below)

Note 1: NIH-managed projects may include partnership development, convening of key stakeholders, program development, coordination, and/or administration, fundraising or fund distribution, reporting as required by donors, etc.

Note 2: FNIH-managed projects may include services above in Note 1 but, in addition, could include management of external collaborations such as creating a grant/contract framework for the selection of award(s), managing the application and peer review process, managing the grant/contract administration (e.g., budget, contracting, tracking of milestones, payments, renewal); ongoing financial monitoring and oversight;, communication/media support; alliance management such as developing and managing policies and procedures (e.g., IP, data access, and confidentially), facilitating scientific collaborations within the project and the reporting of overall scientific and/or financial activities to the donor(s).

17. How can the FNIH complement the activities of the NIH IC on this project? Identify the services that the FNIH is being asked to provide.

18. What is the expected timeframe for FNIH involvement? Is this a one-time event or on-going relationship? (Be as specific as possible with start and end dates.)

F. Partners and Partner Interactions

19. Identify the private partner(s), if any, to date and their contact information. Identify any other partners that are likely to become involved. (private partners can include industry, non-profit organizations, academic institutions, associations, societies, etc.)

20. Identify any additional private funders that might have an interest in this project and could provide possible support, or have provided support to similar projects. These can include individuals, foundations, businesses, other industry partners, associations, organizations, societies, etc.

21. Describe the nature of your (or other NIH staff) interactions (e.g., frequency, type of interaction via email or phone, timeframe of interaction) with potential partners prior to filling out this application. For each partner, please answer the following questions:

    a. Have staff within the IC had email exchanges or phone conversations with possible partners?
    ☐No ☐Yes ☐Unsure
    Description of interaction:

    b. Have staff within the IC personally interacted[4] with possible partners?
    ☐No ☐Yes ☐Unsure
    Description of interaction:

    c. Have staff within the IC discussed common scientific goals[5] with possible partners?
    ☐No ☐Yes ☐Unsure
    Description of interaction:

    d. Have staff within the IC discussed scientific data[6] with possible partners?
    ☐No ☐Yes ☐Unsure
    Description of interaction:

    e. Have staff within the IC discussed funding goals with possible partners?
    ☐No ☐Yes ☐Unsure
    Description of interaction:

22. How will key decisions be made in the proposed partnership (e.g., NIH makes all scientific and management decisions; NIH makes all scientific decisions; a board of advisors including NIH and partners makes decisions)?

23. Do you anticipate that your project will need to establish any governance structures (e.g., Steering Committee, Executive Committee, Scientific Committee)? If so, please outline possible structures in

[4] For example, at meetings, conferences or events hosted by a third party or in meetings scheduled to discuss a possible partnership.
[5] In this context, scientific goals can include unaddressed needs in the field or individual partner goals or missions.
[6] In this context, scientific data can be taken to include preliminary, unpublished data already collected for this project or in preparation for this project.

as much detail as possible (membership, purview, decision makers, etc.). Describe mechanisms for transparency and preventing or mitigating possible conflicts of interest within the governance structures.

24. What are the possible benefits (short- and long-term) for potential private-sector funders? Could there be potential conflicts of interest? What strategies will be used to mitigate potential conflicts (e.g., governance structure, recusal or prohibition from decision making, transparency mechanisms)?

G. Budget

25. Please provide a total budget for the project, detailing expenses and timelines. Specifically identify NIH's contributions (both NIH appropriated funds and in-kind support) for the life of this project as well as the amount of funding that FNIH is requested to raise.

26. Please describe the support (monetary, assets (data, analysis), etc.) desired from private partners, including timelines, for the life of this project.

H. Assessment

27. What will be indicators of success (outcomes) of this project? What are the methods for measuring success? After the partnership has completed all the above activities, what will this project have accomplished?

I. Additional Information

28. Please provide any additional information that would assist the FNIH in evaluating this project and determining how they can be most effective.