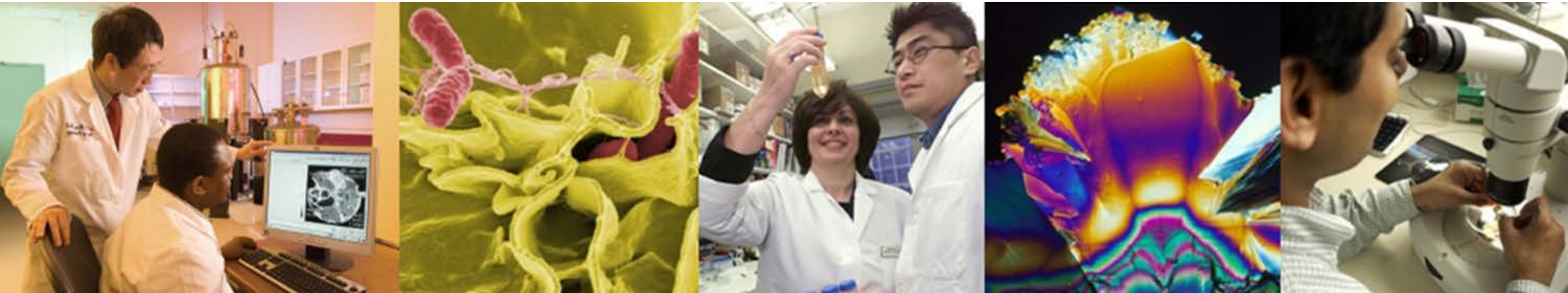


Report of the ACD Working Group for Review of the Moderate Alcohol and Cardiovascular Health Trial

*116th Meeting of the Advisory Committee to the Director
June 15, 2018*



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Review of the Moderate Alcohol and Cardiovascular Health (MACH) Trial

- Introduction
- NIH/NIAAA staff interactions with industry to gain program support
- NIH/NIAAA staff interactions with select extramural investigators
- Peer review process
- Scientific premise of the trial
- Analysis of NIAAA scientific portfolio
- Roles of the Foundation for the National Institutes of Health (FNIH)
- Working Group Recommendations to the NIH Advisory Committee to the Director (ACD)
- Follow-up discussions with NIH Institute and Center Directors (ICDs)

Introduction

- The Moderate Alcohol and Cardiovascular Health Trial (MACH15) is 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 is 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).

Introduction (cont.)

- **Scope of the reviews**
 - I. Circumstances that led to securing private funding for the MACH trial
 - II. The scientific premise of and the planning for the MACH trial
 - III. The processes used to reach the decision to support the MACH trial
 - IV. Program development and oversight once funding was secured by the FNIH
 - V. A review of the NIAAA portfolio prior to and during the current Institute leadership
- **Two, independent but complementary reviews, were conducted**
 - The NIH Office of Management Assessment (OMA) – focused largely on issues I and III
 - A working group of the ACD – focused largely on issues II-V

Introduction (cont.)

- Roles and responsibilities for Program Officers include:
 - “Exercise good stewardship over Federal resources that avoids an actual or apparent financial or intellectual conflict of interest ... knowledge of applicable laws, regulations, and policies ... knowledge of the IC’s mission and program priorities” (GAM Chapter 4.1.04.204)
 - Adhere and promote Principles of Ethical Conduct for Government Officers and Employees including commitments to “act impartially and not give preferential treatment to any private organization or individual” (<https://ethics.od.nih.gov/principl.htm>)
 - As a federal employee, neither misuse his/her position nor “allow the improper use of nonpublic information to further his own private interest or that of another, whether through advice or recommendation, or by knowing unauthorized disclosure” (5 CFR Part 2635.703)

NIH/NIAAA staff interactions with industry to gain program support

- The ACD WG did not assess violations of NIH policy or federal regulations, which was under the purview of OMA
- However, to understand the context that led NIAAA to embark on the MACH trial, the ACD WG considered the nature and extent of interactions among NIAAA staff, select extramural investigators, and industry representatives before FNIH received approval to secure funding for the MACH trial
 - There was frequent email correspondence among these parties which appear to be an attempt to persuade industry to provide funding for the MACH trial
 - Several members of NIAAA staff hid facts from other NIAAA staff and the FNIH
 - The early and frequent engagement with industry representatives calls into question the impartiality of the process and thus, casts doubt that the scientific knowledge gained from the study would be actionable or believable

NIH/NIAAA staff interactions with select extramural investigators; Peer review process

- There were sustained interactions (from at least 2013) between the eventual Principal Investigator (PI) of the MACH trial and three members of NIAAA leadership prior to, and during development of, FOAs for planning and main grants to fund the MACH trial
 - These interactions appear to have provided the eventual PI with a competitive advantage not available to other applicants, and effectively steered funding to this investigator
- An NIAAA senior staff member advised the investigator how to respond to the peer review critiques, including the recommendation to ignore comments of one peer reviewer who raised concerns related to alcohol industry interpretation of trial results

Scientific premise of the trial

- Interactions among several NIAAA senior staff members and industry appear to intentionally bias the framing of the scientific premise in the direction of demonstrating a beneficial health effect of moderate alcohol consumption
- Independent review by two NIH staff members, with considerable experience in epidemiology studies, raise the following concerns:
 - There are insufficient patients and not enough follow-up time to allow for meaningful assessment of cancer endpoints, thus the trial could show benefits while missing the harms
 - The composite primary end-point does not include heart failure; alcohol consumption is associated with a higher risk of heart failure
 - It is inadequately powered to assess long-term safety and overall systemic health status
- Peer reviewers also noted concerns about inadequate power to detect important adverse outcomes (including cancer)

Analysis of NIAAA scientific portfolio

- Modeling of the scientific topics supported by NIAAA over the past 10 years reveals no significant changes in the major topics funded
 - The topic that experienced the most decline between FY08/09 (35 awards) and FY16/17 (8 awards) was the *Sociology of Healthcare*; topics in this group focus primarily on alcohol policy environment (including zero tolerance programs), youth drinking, and the deleterious social effects of alcohol abuse
- However, projects classified as *Alcoholism, Alcohol Use and Health*, one of NIH's standard categories for annual reporting of funding, revealed an overall increase in funding over the past 4 years
 - However, projects related specifically to Alcohol Advertising show a decrease in the level of support between 2002 and 2018
- It is not uncommon for the the portfolio of an NIH Institute to change over time reflecting the need to support newly emergent scientific opportunities

Roles of the FNIH

- Public Private Partnerships (PPP) are a key means to advance science through leverage of public funds with industry contributions which can take the form of intellectual input, in-kind research equities (e.g., small molecules), financial resources
- The FNIH, created by Congress, exists to create an appropriate “firewall” between public funds and private resources, to protect scientific integrity
- A well-established policy requires that NIH staff engage FNIH through a formal *Request for Collaboration* (RFC) vetted first by the Office of Science Policy FNIH Proposal Review Committee, then by the NIH-FNIH Steering Committee
 - An RFC was submitted by NIAAA staff two years after initial contacts with industry representatives
 - However, in response to the RFC requirement to *describe past activities and progress to date for the proposed project, including initial meetings, established collaborations or committees, and grants/contracts funded*, only descriptions of the planning grant and a conference grant were provided
- Following the decision to support a program as a PPP, the FNIH puts into place an Memorandum of Understanding (MOU) that appropriate oversight is provided to preclude inappropriate influence from the funder on the results of the program
 - A robust FNIH-NIH MOU was executed

Working Group Recommendations to the NIH Advisory Committee to the Director

- Support the NIH Director's decision to suspend the MACH trial
- Recommend that the 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)
- 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)

Follow-up discussions with NIH ICDs

Discussion