

NIH Advisory Committee to the Director (ACD)

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

June 2018 Report

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# Advisory Committee of the Director Working Group Report

## Introduction

Prompted by internal concerns raised by current NIAAA leadership, FNIH leadership, and reports in the press, the Director of NIH requested reviews of the Moderate Alcohol and Cardiovascular Health (MACH) trial, including: (i) the circumstances that led to securing private funding for the Moderate Alcohol and Cardiovascular Health (MACH) trial; (ii) the scientific premise of and planning for the MACH trial; (iii) the process used to decide to support the MACH trial; (iv) program development and oversight once funding was secured by the secured by the Foundation for NIH (FNIH); and, (v) a review of the NIAAA portfolio prior to and during the leadership of the current NIAAA Director to assess what programmatic shifts, if any, could be discerned.

Two separate reviews were performed. The NIH Office of Management Assessment (OMA), focused largely on whether there were any violations of NIH policy or federal regulations in either securing private funding for the MACH trial (item i), or during the process used to decide to support the MACH trial (item iii). A complementary review was conducted by a working group of the NIH Advisory Committee to the Director (ACD working group), focusing largely on items ii-v. Both the OMA and ACD working group reviews were informed by extensive fact-finding conducted by staff within the Office of the (NIH) Director.

## Executive Summary

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).

The NIH Director charged a working group of the Advisory Committee to the (NIH) Director (ACD) 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.

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 to

support the trial. There was early and frequent engagement among these parties which appear to be an attempt to persuade industry to support the project. Several members of NIAAA staff kept key facts hidden from other institute staff members and the FNIH. The nature of the 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.

There were sustained interactions between the eventual principal investigator of the MACH trial and members of the NIAAA leadership prior to and during the development of FOAs for planning and main grants to fund the program. These interactions appear to have provided the eventual principal investigator with a competitive advantage not available to other applicants, and effectively steered funding to this investigator.

Interactions among several NIAAA staff and industry representatives 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 of the trial plan raised concerns that there are insufficient patients and not enough follow-up time to allow for meaningful assessment of cancer endpoints. The composite primary endpoint does not include heart failure. Thus, the trial could show benefits while missing harms.

Modeling of the scientific topics supported by NIAAA over the past decade does not reveal any significant changes in the major topics funded. Projects classified as *Alcoholism, Alcohol Use and Health*, one of the NIH's standard categories for annual reporting of funding, revealed an overall increase in funding over the past four years; however, projects related to Alcohol Advertising show a decrease in the level of support from 2002 to 2018. It is not uncommon for the portfolio of an NIH institute to change over time reflecting the need to support newly emergent scientific opportunities.

Public private partnerships (PPPs) are a key means to advance science through leverage of public funds with industry contributions. The FNIH, created by Congress, exists to create an appropriate "firewall" between public funds and private resources, in support of scientific integrity. NIAAA staff did engage FNIH with a formal request for collaboration but failed to adequately report prior initial meetings and discussions with industry. A robust FNIH-NIH memorandum of understanding was executed to ensure that an adequate firewall was in place.

The ACD WG recommends to the ACD that:

- The NIH Director's decision to suspend the MACH trial be supported
- 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)

- The NIH should examine additional measures to assiduously avoid providing an advantage, 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)

## I. Working Group Report

### A. NIH/NIAAA staff & investigator interactions with industry to gain program support

While it is not under our purview as the ACD working group to assess violations of NIH policy or federal regulation, it is sensible to consider the context that led to NIAAA embarking on a large multi-site clinical trial to examine the cardiovascular health effects on moderate drinking. In particular, we wished to assess the nature and extent of interactions among NIAAA staff, extramural investigators (including the eventual PI of the MACH trial), and industry representatives<sup>1</sup> before the FNIH received approval to secure funding for the MACH trial. Frequent email correspondence among members of NIAAA senior staff, select extramural investigators (including the eventual PI of the MACH trial), and industry representatives (Appendix Item E, pp. 27-77, and pp. 93-117) occurred prior to involvement of the FNIH and the development of the NIH funding opportunity announcement (FOA) for a multi-site clinical trial on moderate drinking and cardiovascular health. These communications appear to be an attempt to persuade industry to provide funding for the MACH trial.

Moreover, these senior members of NIAAA staff appear to have purposefully kept other key members of NIAAA staff and the FNIH ignorant of these efforts. For example, correspondence between NIAAA staff draws attention to a February 2014 wine industry blog that reports that FNIH is initiating a search for industry funding to support a major clinical study on the health effects of moderate alcohol consumption (pp. 50-60). One senior staff member at NIAAA is unaware of any such potential planning, asking another senior staff member about the article "... Anything seem broken here?" (p.55), even though such a trial to test moderate drinking effects on cardiovascular health should very likely involve the programmatic division to which this senior staff member belongs. In response to receiving the forwarded discussion, NIAAA senior leadership communicates among one other, "Best not to respond right now but we can't keep him totally in the dark." (p.54), and then later provides an email response to a senior staff member [from the communications office] stating they have not asked industry to fund a study and, "We have no plans to engage in such a trial." (p. 50) This information is then relayed to FNIH.

<sup>1</sup> Most commonly mentioned industry representatives were from DISCUS, DIAGEO, ICAP, and IARD. In addition, the Beer Institute, Spirits EU, and Wine Institute were also among the discussants.

There is also significant concern that the early and frequent engagement of industry representatives calls into question whether scientific knowledge gained from the study results would not be actionable (adoptable into clinical recommendations) or believable (by either clinical stakeholders or the public). This is further covered in Section D. Scientific premise of the trial, below.

## B. NIH/NIAAA staff interactions with select extramural investigators

### *1. Interactions during the funding opportunity announcement (FOA) development and application process*

NIH program staff typically engage with the applicants and potential applicants to answer their questions about which funding opportunity they should apply to, depending on their proposed research, scientific interest, or administrative aspects of their proposed research plan (for example, estimated budget, or length of time needed to complete the study). A review of related email correspondence (Appendix Item E, pp. 74-80) reveals significant irregularities and deviations from normal practice.

There were sustained interactions, beginning in 2013, between the eventual PI of the MACH trial and members of NIAAA senior leadership. These interactions took place well before and throughout the development of the funding opportunity for the planning grant (U34) and main grant (U10). For example:

- In 2013, the eventual PI of the MACH trial was included in discussions such as which funding mechanisms and activity codes could be used to support the full multi-site clinical trial. (pp. 75-76)
  - one of the NIAAA senior staff members writes about past collaborative projects with “involvement of NIAAA staff (me).” and describes, “The fact that we competed these did not get in the way of ultimately having the grants go to those we wanted them to go to,....” , (p.75)
- In 2013, correspondence between two NIAAA senior staff members involved with the development of the U34 funding opportunity announcement clearly indicated their intent to travel on their “personal time” to work directly with the eventual U34 awardee on his application. (p. 79)
- In 2015, during the development of the U10 FOA to announce applications to the MACH trial, NIAAA program staff updated the eventual PI of the MACH trial as to the structure of the application, the likely date the FOA would be made public, and the likely due date of the application. (pp. 80)

These violate well-established and posted NIH staff principles applicable to program staff, that “Employees shall act impartially and not give preferential treatment to any private organization

or individual.”<sup>2</sup> Furthermore, taken together, these interactions appear to have greatly influenced who would eventually receive funding to support the MACH trial.

## *2. Development of Planning Grant (U34) FOA*

On July 12, 2013, an NIH Guide notice ([NOT-AA-13-004](#) “Notice of NIAAA's Participation in PAR-11-169 ‘Clinical Trial Planning Cooperative Agreement (U34)’”) was published to announce that NIAAA intended to participate in (or, “sign on to”) an existing FOA from another institute (NIAMS U34 planning grant [PAR-11-169](#) “NIAMS Clinical Trial Planning Cooperative Agreement”). The practice of signing on to an existing FOA itself is not unusual – institutes often “sign on” to an FOA in order to potentially fund incoming applications to that FOA, in particular for areas of mutual scientific interest. However, in this case, the announcement by NIAAA invites applications to support planning for “feasible and well-designed multicenter clinical trials focused on the effects of moderate consumption of alcohol (as defined by NIAAA guidelines) on the decreased or increased risk of certain chronic diseases”. In addition, planning grant announcements usually do not seek applications for a specific trial but are rather more open-ended. Furthermore, in the context of email discussions among NIAAA staff (pp. 74-78), it appears that this approach was used to circumvent standard operating procedures and reduce the time for applications in response to NIAAA’s July 12 “sign on”.

We reviewed archived internal records (Appendix Item I, (pp. 124-126)) that show that in submitting the notice for publication in the NIH Guide for Grants and Contracts, NIAAA initially requested an NIAAA-specific due date (September 15, 2013), which would have given the minimum required time window (60 days) for applications to be submitted for consideration by NIAAA. This request, rather than using the pre-established due dates from the NIAMS announcement was not approved in central NIH review by the Office of Extramural Research (OER) and Center for Scientific Review (CSR) through the Guide review process. As a result, the opportunity for NIAAA U34 planning grant funding through [NOT-AA-13-004](#) used due dates available in the existing NIAMS announcement ([PAR-11-169](#)), and was available to the public for a more substantial period of time to allow incoming applications (July 13, 2013 through a November 1, 2013 due date) than had been requested by NIAAA staff.

Archived internal records from the review of the U34 “sign on” FOA also show NIAAA had included language to describe a pre-approval process, where incoming applications would have to be pre-approved by NIAAA before submission. This pre-approval process is not permitted except for applications with budgets requesting over \$500k in (see [NOT-OD-02-004](#)), thus in the course of the NIH Guide review, this pre-approval language that had been requested by the NIAAA staff was rejected.

While the resultant NIAAA U34 funding opportunity was available to the public for a substantial period of time to allow incoming applications (111 days), taken in the context of email correspondences, the sign-on to the NIAMS U34 to expedite announcing the funding

<sup>2</sup> “Principles of Ethical Conduct for Government Officers and Employees” <https://ethics.od.nih.gov/principles.htm>

opportunity publication indicates the intent to circumvent normal timelines for funding opportunity development, and to limit applications, such that it would favor a pre-selected PI.

Supporting email correspondences, shown in Appendix Item E, (pp. 74-80) include:

- a) emails from NIAAA staff regarding funding strategy that cc: the eventual PI (pp. 75-76) , and
- b) emails among the NIAAA senior staff members indicating intent to choose this route to avoid NIH Office of the Director/Office of Extramural Research “bureaucratic timeframe of getting our own out there” (p. 77), and that “I think the PI can easily meet that, given that we have gone over in a lot of detail what the ultimate RCT should look like; plus that tight a timeframe would discourage other applicants who have not even begun to think about this idea yet !” (p. 78)

### *3. Development of U10 Clinical Trial Funding Opportunity Announcement*

The ACD working group reviewed NIH Guide documents related to the clinical trial U10 funding opportunity announcement (FOA) ([PAR-16-363](#) – “Multi-Site Randomized Controlled Clinical Trial Research Center on Alcohol's Health Effects”), through which the MACH trial was funded. (Appendix Item I, pp. 127-128) While the resultant published funding opportunity announcement allowed open competition and ample response time to submit applications, internal documentation supports an attempt to continue the limitation of the applicant pool, as discussed above in section B.2.

The draft of [PAR-16-363](#) was originally requested by NIAAA to be published by the NIH Guide as a limited competition (pp. 127-128), requiring the aforementioned U34 planning grant in order to apply for this new, main clinical trial FOA. The request to issue this as a limited competition was turned down in internal FOA review processes by the Office of Extramural Research, with the recommendation that issuing this FOA as a limited competition was not justified; however, the FOA could request including data obtained from the U34 planning grant stage in the U10 application. As a result, the published funding opportunity [PAR-16-363](#) states that, *“Applicants for the U10 Clinical Trial Implementation Cooperative Agreement must be able to begin the trial without further planning activities when the U10 is awarded. Therefore, investigators who have already completed planning activities through an NIAAA-funded U34 clinical trial planning grant are expected to apply.”* and *“The purpose of this FOA is to encourage applicants who have completed clinical trial planning activities and development of clinical trial infrastructure, through NIAAA-funded U34 Randomized Controlled Trial planning grants or other funding sources, related to the investigations of the effects of alcohol consumption on neurological diseases, particularly stroke, and health issues associated with aging.”*

This practice of issuing a planning grant to support applications to a major clinical trial is in itself is not unusual. Several institutes and centers have used U34 planning grants in this way, as two-phase process for seeking applications for major clinical trials. For examples, see the “FOA Purpose” section of [PAR-12-124](#), and “Eligibility” section of [PAR-11-157](#). Note that, in both examples, there are options to request a waiver if planning activities were supported by other



means. Current NIH Guide review practices, in effect as of 2014, are that funding opportunities should not be limited to only prior planning grant recipients but should allow applications from those who have met the planning needs by other means, regardless of source of support.

As aforementioned, NIH policy requires that funding opportunities must be made available to the public for at least 60 days before the due date (for new FOAs). The U10 FOA ([PAR-16-363](#) – “Multi-Site Randomized Controlled Clinical Trial Research Center on Alcohol's Health Effects”) was open for 96 days, which does comply with NIH requirements.

As described in the next section, a) only one U34 planning grant application was received and reviewed by NIAAA in response to their U34 sign-on Notice, and b) only one U10 application was received and reviewed in response to the U10 FOA. Both applications had the same lead principal investigator, who, as described in above, was frequently engaged in conversations by members of NIAAA senior staff.

While both funding opportunities were available for open competition for the required minimum of 60 days, it appears highly likely that the interactions between NIAAA senior staff members with the single, extramural investigator: 1) heavily influenced that investigator’s ability to quickly submit responsive applications, 2) provided the investigator a competitive advantage not available to other applicants, and 3) effectively steered funding to the PI of these staff members’ choosing.

### C. Peer review process

We reviewed the full MACH trial application, and other applications related to the trial, including the 2014 U34 planning grant ([U34 AA023258](#)), and two conference grants ([U13 AA023452](#) funded in 2014, and [R13 AA025838](#) funded in 2017).

#### *1. Primary review of the grant applications*

We reviewed the peer review rosters for the study sections that reviewed these grants, and the lists of applications reviewed by Special Emphasis Panels (SEPs) in response to both NIAAA’s sign-on to the U34 clinical trial planning grant FOA, and the U10 FOA.

In 2014, the NIAAA SEP “[Review Of PAR-11-169 NIAAA U34 Applications](#)” reviewed two applications – the U34 application submitted in response to the NIAAA sign-on, and a U13 application submitted to a parent conference grant FOA ([PA-13-347](#)) (‘Parent conference grant’ referring to a trans-NIH/multi-IC request for investigator-initiated conference grant topics). Both applications were submitted by the same investigator, who was the eventual PI of the MACH trial. The review of these two applications by this single SEP is not outside the norm of NIH practice.

In 2016, the SEP “[Multi-Site Randomized Controlled Clinical Trial Research Center On Alcohol's Health Effects](#)” reviewed only one application (and its subprojects).

Email correspondence between the investigator and an NIAAA senior staff member (the eventual program officer for the planning grant, and eventual NIAAA project scientist on the U10/MACH trial) indicates that this senior staff member advised the applicant on how to respond to peer reviewer critiques, including providing recommendations that go beyond programmatic staff responsibilities, such as to ignore comments of one peer reviewer who raised concerns related to alcohol industry interpretation of trial results. (pp. 82)

Thus, throughout the inception, development and awarding of the MACH trial, there was an unusually close and inappropriate set of interactions between NIAAA senior leadership, and the investigator ultimately selected as the PI of the MACH trial. These close interactions span from the inception of the plan to secure industry sponsorship, through the planning and development of the NIAAA FOAs, culminating in the process of helping the PI respond to study section critiques.

## *2. Secondary Council review*

As required, in addition to a first-level review by a peer review study section, applications to NIH also undergo a secondary level of review by the National Advisory Councils. The process for NIAAA Advisory Council Review is described in Appendix Item H (pp. 121-123) which was provided to the working group for background. The working group also reviewed the agenda of the Council session and documentation related to the Council session, such as the comments by an NIAAA senior staff member to introduce the proposed project to the council (Appendix Item J, pp. 129-132), and email correspondences discussing the Council review (Appendix Item E., pp. 83-92). The closed council session was held on April 20, 2016 by teleconference.

The NIAAA senior staff member who frequently advised the eventual PI of the MACH trial (as described in Section C.1., above) introduced the application to Council. After the Council meeting, this same individual provided other NIAAA leadership with a rebuttal to comments from at least two Council members, one who was not able to attend the teleconference raised concerns about the trial design (pp. 86-89). A comment in the correspondences reviewed indicated that the vote of the Council member who could not call in to the Council teleconference did not count, since he was not on the call (pp. 83-84). It is a standard NIAAA practice that only Council members who participate in the meeting can vote, to ensure that all voters have participated in the active discussion, and then take this discussion into account when placing their vote. The standard procedure of having quorum for the meeting to take place was also upheld in this Council Review.

## *D. Scientific premise of the trial*

We acknowledge that the question of whether moderate drinking benefits health is an interesting one to ask, given the public interest in the issue, but difficult to answer. However, apart from the methodological challenges described below, the appearance of industry involvement with the design of the study, and the perception of conflict that this entails, would

weaken any potential beneficial findings that might emerge. Email correspondence (Appendix Item E, pp. 93-117) clearly shows industry interactions and discussions related to the scientific planning of the study that appear to go beyond the norm:

- September 2013 email from leadership of Spirits EU to NIAAA senior staff noting interest in proposed work NIAAA plans on a conference on the benefits of alcohol and “clinical trials to show the J curve in all its glory”. (p. 95)
- July 17, 2014 email from NIAAA senior leadership to NIAAA staff addressed “Dear team health benefits of drinking” (p. 97)
  - States inclination not to raise a BMJ essay by Glymour, et al. with “Building 1” unless specifically asked
    - The essay referenced (Glymour, 2014) is a comment on a 2014 BMJ paper (Holmes et al., 2014) concluding that “Individuals with a genetic variant associated with non-drinking and lower alcohol consumption had a more favourable cardiovascular profile and a reduced risk of coronary heart disease than those without the genetic variant. This suggests that **reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health.**”
  - August 4, 2014 emails between the eventual PI of the MACH trial and ICAP (International Center for Alcohol Policies (ICAP), a non-profit sponsored by alcohol producers.) – the investigator provides responses to address methodological issues raised by Diageo, DISCUS, ABI, and ICAP (pp. 100-110)
  - December 8, 2014 conference call to discuss study attended by NIAAA senior staff and the PI, with ICAP board members (and representing 12+ alcohol distiller/manufacturer/distribution companies) invited (pp. 111-115)
  - February 26, 2015 Email from a NIAAA senior staff member and the investigator, asking for edits to the NIAAA staff member’s draft email (likely to ICAP) which includes a bullet that states ‘one of the important findings will be showing that moderate drinking is safe’. (pp. 116-117)

These interactions would undermine the perception of study objectivity and would call into question any potential findings that may show a beneficial effect of moderate drinking on cardiovascular health.

The ACD working group members suggested additional review of the clinical trial design by epidemiologists, particularly given a recent meta-analysis and commentary published in Lancet (Connor & Hall, 2018; Wood et al., 2018) on risk thresholds for alcohol consumption.

Consequently, NIH asked two members of NIH staff with expertise in epidemiology to review the study design: Michael S. Lauer, MD (current Deputy Director for Extramural Research, former director of NIH NHLBI Cardiovascular Program Division) and Barry S. Kramer, MD (Director of the Division of Cancer Prevention at the National Cancer Institute.)

A summary of their reviews is included in the Appendix Item F (pp. 118-119). In brief, they noted that the concept of conducting an alcohol randomized clinical trial is not inherently

unethical. There is an element of equipoise and the authors of a recent Lancet meta-analysis (Wood et al., 2018) state this. Both, however, would not recommend this study as designed. Specific issues noted include:

- There are not enough patients and not enough follow-up time to allow for meaningful assessment of cancer endpoints so that, the trial might show benefits while missing the harms
- It is inadequately powered to assess long-term safety and global health status
- The composite primary endpoint does not include heart failure, which is a serious shortcoming. Alcohol consumption is associated with higher risk of heart failure; there is even a well-described “alcoholic cardiomyopathy.”
- The premise contradicts recent scientific reports on the association between alcohol intake and cardiovascular health, for example:
  - a recent Mendelian randomization study suggests that lower levels of alcohol consumption, even starting at moderate levels, is associated with lower (not higher) risk of cardiovascular events (Holmes et al., 2014) (note that this work was available prior to the funding decision)
  - a 2018 Lancet meta-analysis (Wood et al., 2018) finds an increased mortality risk at doses of 100 g/week. The MACH trial calls for doses of 98 g/week, potentially indicating that even a slight error in dosing might be expected to cause increased mortality risk – (note that this work was not available prior to the funding decision).
- The cost of the trial is large, relative to the limited yield
- The grant as written suggests that the authors do not have the requisite equipoise

Several of these same issues were also identified in the critiques submitted as part of the standard peer review process. Peer reviewers noted that the issue of moderate alcohol effects on cardiovascular health is an important question, and a randomized clinical trial would be the best way to answer the question. However, issues raised by reviewers included the concerns about long-term compliance and about inadequate power to detect important adverse outcomes (including cancer), noting that its outcome could be misinterpreted to show no effect of alcohol on cancer.

#### [E. Analysis of the NIAAA portfolio](#)

We requested information on any strategic shifts in relation to the NIH portfolio of a whole. We reviewed information related to NIAAA funding priorities, including Institute strategic plans (2009-2014 and 2017-2021 strategic plans), portfolio analyses on NIAAA funded grants, and NIH grants to support research into alcoholism.

In the analyses provided as part of Appendix Item L.1 (pp. 150-160), the evolution of the NIAAA portfolio was quantified over the past ten fiscal years, modeling NIAAA scientific topics by using word2vec, a computational method that maps documents in multidimensional vector space

based on their semantic content. and then partitioning NIAAA awards into topically defined clusters across the word2vec map of the entire NIH portfolio. The analysis specifically focused on NIAAA Type 1 (“new”) and Type 2 (“renewal”) Research Project Grant (RPG) awards for fiscal years (FY) 2008 through 2017. The resulting images, which were generated with the Cytoscape tool, display the distribution of NIAAA RPG awards across all topic clusters in each year. The accompanying spreadsheet displays the number and percentage of NIAAA RPG awards in each cluster made in each year of the FY08-FY17 time frame. Using this method, no changes in major topics were identified. The scientific topic with the most significant NIAAA funding decline over the period analyzed was the “Sociology of Healthcare” (93 NIAAA awards from FY08 through FY17, of which there were 35 in FY08/FY09 and 8 in FY16/FY17) (p. 160) The 93 NIAAA awards in that cluster focused primarily on the alcohol policy environment (including zero tolerance programs), youth drinking, and the deleterious social effects of alcohol abuse.

Additional analyses using text mining to visually categorize and cluster words and multiword phrases (in conjunction with NIH-wide definitions used to match projects to categories) also did not indicate changes in major topics.

We also looked at funding and number of awards for projects classified as “Alcoholism, Alcohol Use and Health”, one of NIH’s standard [categories for annual reporting](#) of funding towards particular research areas, diseases, or conditions Across NIH, the total amount of funding towards projects classified as “Alcoholism, Alcohol Use and Health” increased in the past four years. (Appendix Item L.2, pp. 162-163: Alcoholism funding: NIAAA and NIH-wide)

We also looked at reporting on NIAAA projects related to “Alcohol advertising” . (Appendix Item L.3, p. 164) Using the search terms “alcohol advertising” or “advertising” to search funded and pending NIAAA awards, during the time period examined (FY2002 to FY2019<sup>3</sup>), the level of support has changed, with the most studies supported between FY08-13, and the fewest studies between FY14-19. In FY2002-2007, most projects on this topic came from unsolicited applications. Four of the new projects from the 2008-2013 timeframe also resulted from unsolicited applications. In FY 2011, a program announcement (PA) was issued for “Alcohol marketing and youth drinking” ([PA-11-015](#)). Three of the newly funded projects in FY2008-2013 responded to this PA, which expired May 8, 2014. Other PAs that yielded new projects in this area from 2008-20113 included ones for epidemiology and prevention in alcohol research ([PA-07-448](#); currently active), secondary analysis of existing alcohol epidemiology data ([PA-08-167](#); currently active), science of behavior change ([RM-10-002](#); expired April 2010), and structural interventions for alcohol use and risk of HIV/AIDS ([PA-07-005](#); expired May 2016). Although no new projects were funded in FY14-19, ongoing support for previously awarded projects continued.

It is not unusual for Institute research portfolios to evolve over time. This typically reflects the emergence of new opportunities that necessitate a reprioritization of the current portfolio mix.

<sup>3</sup> Results up to May 18, 2018 are included in the analysis, thus FY19 data is not final as NIH continues to accept applications for this fiscal year.

## F. Foundation for the National Institutes of Health (FNIH) processes

Public-private partnerships are one key means to advance science through leveraging taxpayer-supported research with private contributions which can take the form of intellectual input, in-kind equities (e.g., biosamples, small molecules), or financial resources. The FNIH, created by the Congress, creates an appropriate “firewall” between private resources, and public funds, to prevent conflicts which could otherwise influence the result of a research study in a manner which benefits the private donor.

In the case of the MACH trial, in opposition to NIH policy, NIAAA staff directly engaged with industry representatives, accompanied by extramural researchers, over two years prior to the FNIH’s involvement, and in a manner that kept FNIH and some members of NIAAA staff in the dark, as described above in Section A. NIH/NIAAA staff & investigator interactions with industry to gain program support.

While we did not identify issues regarding program development and oversight once funding was secured by the FNIH, and a robust Memorandum of Understanding (MOU) for NIAAA clinical trial funding was issued and executed, we examined aspects of the FNIH-NIH collaboration process to identify potential areas for NIH to review in further detail, and to consider additional checks that may be put into place as part of the FNIH-NIH Request for Collaboration process. As part of our working group review, we reviewed documentation describing the Request for Collaboration process (Appendix Item K.1, pp. 133-134, the Request for Collaboration form for a Multisite Randomized Trial of Health Effects of Moderate Drinking (Appendix Item K.2, pp. 135-141) and the signed FNIH-NIH Memorandum of Understanding for this trial (Appendix Item K.3, pp. 142-149).

The FNIH-NIH process is described in Appendix Item K.1, pp. 133-134 “Information on FNIH-NIH Request for Collaboration process”. In summary, the protocol in place for the past several years includes 1) an application for FNIH partnership through a Request for Collaboration form, 2) Review of Requests for Collaboration (RFC) by the NIH Office of Science Policy (OSP), 3) Request for Collaboration Review by FNIH-NIH Steering Committee, and 4) Request for Collaboration Review by FNIH.

Several key criteria are explicitly evaluated by the OSP review committee (using a score sheet). They include whether the project is:

- 1) Mission-Appropriate
  - a. Consistent with NIH’s mission and aimed at advancing one or more of its goals
  - b. Not involving an organization that has a mission contrary in purpose to NIH or the US government
- 2) Value-Added
  - a. Of clear benefit to NIH and its ICs and meets an unaddressed need

- b. Non-duplicative of efforts underway at NIH, unless a sufficient justification is given
  - c. Leveraging resources across multiple sectors with synergistic effect
- 3) Practicable
- a. Proposal concept is well defined with achievable milestones and a timeline for completion
  - b. Cannot be accomplished by NIH mechanisms (e.g., gift funds)

The FNIH-NIH Steering Committee considers these factors (and receive the score sheet for their information), and also considers the overall application and its suitability for partnership with FNIH.

As part of the Request for Collaboration form, information is sought in questions 3f and 3g to identify potential partners, which may include people from industry, academic institutions, associations, foundations, societies, etc. (See Appendix Item K.2, pp. 137-138.) This information is not used by NIH in its review but is transmitted to the FNIH for their information only, should the collaboration request be approved by NIH.

The FNIH-NIH Request for Collaboration for a Multisite Randomized Trial of Health Effects of Moderate Drinking was submitted February 20, 2015, listing the contact information of the NIAAA senior staff member who was the eventual NIAAA staff project scientist on the MACH trial. In this form, NIAAA did indicate that the “International Alliance for Responsible Drinking (IARD) has coordinated commitments from six global alcohol producers” and provides a specific contact name for IARD (p. 137), and also states, “There is also interest from the health insurance industry,” (p. 138) with no additional contact information provided. In response to the collaboration form request to “describe past activities and progress to date for the proposed project, including initial meetings established collaborations or committees, and grants/contracts funded,” (question 3h. in Appendix Item K.2, pp. 138), only the descriptions of the U13 and U34 grants were provided by NIAAA.

## II. Recommendations

The ACD working group recommends that NIH:

- not continue the trial, given:
  - o early and frequent industry interactions to gain support for the study
  - o irregularities in funding opportunity design
  - o actions and emails by members of NIAAA senior staff that communicate their intent to avoid open competition for research funding
  - o actions by members of NIAAA senior staff indicating the intent to effectively pre-select principal investigator of the MACH trial
  - o 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



### III. Papers cited

Connor, J., & Hall, W. (2018). Thresholds for safer alcohol use might need lowering. *The Lancet*, 391(10129), 1460–1461. [https://doi.org/10.1016/S0140-6736\(18\)30545-2](https://doi.org/10.1016/S0140-6736(18)30545-2)

Glymour, M. M. (2014). Alcohol and cardiovascular disease. *BMJ*, 349, g4334. <https://doi.org/10.1136/bmj.g4334>

Holmes, M. V., Dale, C. E., Zuccolo, L., Silverwood, R. J., Guo, Y., Ye, Z., ... on behalf of The InterAct Consortium. (2014). Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ*, 349(jul10 6), g4164–g4164. <https://doi.org/10.1136/bmj.g4164>

Wood, A. M., Kaptoge, S., Butterworth, A. S., Willeit, P., Warnakula, S., Bolton, T., ... Danesh, J. (2018). Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *The Lancet*, 391(10129), 1513–1523. [https://doi.org/10.1016/S0140-6736\(18\)30134-X](https://doi.org/10.1016/S0140-6736(18)30134-X)

## Appendices

- A. Charge to group
- B. Summary of meeting activities
- C. List of resources/materials provided to working group
- D. Timeline of events
- E. Emails reviewed by the working group
- F. Summary of comments from NIH staff epidemiologists' review
- G. Description of NIAAA standard operating procedures for FOA planning and clearance
- H. Description of NIAAA council duties and responsibilities
- I. Documentation related to review of Notice NOT-AA-13-004 and PAR-16-363
- J. Council agenda and comments introducing Council Review of MACH trial
- K. Foundation for NIH (FNIH) materials
  - 1. Information on FNIH-NIH Request for Collaboration process
  - 2. Copy of FNIH-NIH Request for Collaboration memo submitted for funding of a multi-site randomized trial of health effects of moderate drinking
  - 3. Copy of signed NIH/NIAAA-FNIH MOU
- L. Portfolio analyses
  - 1. NIAAA-wide portfolio analyses
  - 2. Alcoholism funding: NIAAA and NIH-wide
  - 3. NIAAA projects related to "Alcohol advertising"

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

## Background

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NIH has entered into a variety of highly successful public-private partnerships (PPPs) through which seemingly intractable and highly significant biomedical research problems have been addressed. For example, the [Accelerating Medicines Partnership \(AMP\)](#) has been an enormously successful PPP between the NIH, U.S. Food and Drug Administration, 12 biopharmaceutical and life science companies, and 13 non-profit organizations. AMP is working to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets for therapeutics in Alzheimer's disease, autoimmune disease (lupus and rheumatoid arthritis), type-2 diabetes, and Parkinson's disease. The [Foundation for the National Institutes of Health \(FNIH\)](#) has been a key partner in such PPPs. They procure funding on behalf of defined NIH activities and manage the partnerships with public and private institutions in support of the NIH mission.

Several epidemiological and basic science studies have suggested that moderate drinking can be beneficial to health by reducing risk for coronary artery disease, type 2 diabetes, and rheumatoid arthritis, among other diseases and conditions. However, these studies used different protocols and are difficult to compare. The National Institute of Alcohol Abuse and Alcoholism (NIAAA) was encouraged to launch a multi-site, multiyear clinical study to clarify the health impact of moderate alcohol consumption via a "Significant Item" from the Joint Explanatory Statement on the Consolidated Appropriations Act of 2015. As a result, NIAAA issued a funding opportunity ([PAR-16-363](#)) for a multi-site randomized trial of health effects of moderate drinking, which was launched in 2016. FNIH was engaged to help support the efforts.

The scientific goals of such a multi-site, randomized clinical trial — to establish an evidence base and provide clear guidelines on the benefits versus the risks of moderate alcohol intake — are worthwhile. The NIH and the FNIH have mechanisms in place designed to protect the integrity of the science supported by donations through the FNIH. For example, NIH completed a Memorandum of Understanding in September 2016 with the FNIH that limits NIH-donor communication in the moderate drinking study. NIH is deeply concerned, however, about reports in the media of what may have happened prior to FNIH's engagement to obtain funding for this trial.

The NIH director assembled a working group of his ACD for an independent review of the scientific planning and administration of the Moderate Alcohol and Cardiovascular Health (MACH) trial, which was funded in response to the funding opportunity PAR-16-363.

## Charge

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This ACD working group members, external to NIH, together with the working group chair, will review the merit and soundness of the scientific planning phases, the administrative approaches used to conduct peer review and ultimately select the trial for support, and oversight of the study since its inception, including records on the development of the funding opportunity, the grant application, peer review results, and other materials as appropriate.

## Structure

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Subcommittee members are selected by the NIH Director. Meetings will be held by teleconference. The working group will report their recommendations to the ACD, with a target reporting date of the June 14-15, 2018 ACD meeting.

## Roster

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- Mark Dybul, M.D.  
Professor and Director  
Center of Global Health and Quality  
Georgetown School of Medicine
- Jay Ashok Shendure, M.D., Ph.D.  
Professor, Department of Genome Sciences  
University of Washington School of Medicine

## CHAIR

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- Lawrence Tabak, D.D.S., Ph.D.  
Office of the Director, National Institutes of Health

## EXECUTIVE SECRETARY

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- Nicole J. Garbarini, Ph.D.  
National Institutes of Health  
Immediate Office of the Director

## Appendix Item B. Summary of meeting activities

In response to the charge from the NIH Director to review the scientific premise and planning of the MACH trial, the working group met via an initial teleconference, to review the charge, documents/literature to be provided to the group, and the questions to consider. The questions raised included whether the study holds scientific value, whether the scientific planning and premise was appropriate, and whether there were any indications of a strategic shift in NIAAA funding priorities that would substantiate public concerns about industry influence in the scientific planning and funding processes. Between the first and second meetings, one member informed the working group coordinators that his spouse received funding for an NIAAA grant, and working group coordinators and the member agreed to recuse from further participation. At the second meeting, the group was briefed by NIH that upon initial review of internal staff correspondence, gathered as part of due diligence review by the NIH Office of the Director, there was a clear indication that there were significant variance from standard practices in the planning and development of the funding opportunity, in the form of interactions with a specific PI prior to the funding opportunity's release. The group was asked the key question, "Should this trial continue based on its scientific value, given that we are now aware of significant process variation?" Points raised by the external members included:

- Given how the trial was being funded, and the existing research of the lead principal investigator (PI) to which the awards were directed to, any outcome of this existing trial will point back to the initial questions and concerns raised by the process abnormalities, given that the lead PI had previously published on the benefits of moderate alcohol consumption.
- A competing concern to stopping the trial was, if it was not done now, will it ever be done? To begin from ground zero it might be manageable, but given the framing caused by the industry interactions, it may call into question the findings of the trial. For example, if it agreed with reports such as a recent Lancet study (Wood et al., 2018), and/or had neutral or negative results, it might be believed. On the other hand, if it finds a benefit associated with moderate drinking and cardiovascular health, the findings will be under question as to whether they could be taken seriously.

The group asked whether any epidemiologists had been consulted, to which NIH provided a brief overview provided in consultation with NIH leadership with background in cardiovascular health, cardiovascular epidemiology (Michael S. Lauer, MD, current Deputy Director for Extramural Research, former director of NIH NHLBI Cardiovascular Program Division), that reviewed the trial design, and said that based on the study design was not powered appropriately, and secondary outcomes are unknowable. The members agreed that the question is important as to whether moderate drinking benefits health, but if it is not powered appropriately, then there is no way for the findings of the study to provide beneficial information. They suggested a second epidemiologist be consulted as well.

In the group's third teleconference, NIH updated the group about the NIH Director's decision to suspend trial activities while the review was underway, briefed the group on additional materials

related to portfolio review, provided the summary of comments from the second epidemiologist asked to review the MACH clinical trial design, and discussed plans for reporting follow up.

The ACD working group members reviewed the draft report and discussed edits and recommendations in two follow-up teleconferences.

[Appendix Item C.: Full list of resources/documents provided to the group](#)

**NIAAA Processes**

- Description of general NIAAA Advisory Council process
- Description of general NIAAA FOA development process

**FNIH-NIH/NIAAA collaboration**

- Request for Collaboration document submitted to initiate
- Signed Memorandum of Understanding (MOU) between FNIH and NIH/NIAAA
- General background on the FNIH-NIH request for collaboration process

**Email correspondences from NIAAA staff related to the planning of the MACH trial**

**Development of funding opportunity for MACH trial (U10)**

- [PAR-16-363](#)
- NIH Guide internal review documentation of the PAR
- Significant Item from the Joint Explanatory Statement on the Consolidated Appropriations Act of 2015

**Additional materials on the topic of moderate drinking**

- Summary of other clinical trials involving “moderate drinking” or “moderate alcohol” as per [clinicaltrials.gov](http://clinicaltrials.gov)
- Review papers on moderate drinking and cardiovascular health
- List of other NIH funded projects on “moderate drinking” (+/- cardiovascular health) as per RePORT
- NIH-funded projects including search terms "moderate alcohol" or "moderate drinking"

**Details of U10AA025286 (MACH) application and peer review**

- Application
- Information on Study Section: Special Emphasis Panel [ZAA1-DD (05)]

ZAA1 DD- (05)	MULTI-SITE RANDOMIZED CONTROLLED CLINICAL TRIAL RESEARCH CENTER ON ALCOHOL'S HEALTH EFFECTS	<a href="#">03/29/16</a>
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Roster:

<https://public.era.nih.gov/pubroster/jsp/preSepIndex.jsp?AGENDA=305811&CID=100185>

- List/number of applications that went to the review
- Notice of award
- Materials related to council session which reviewed the study
  - Agenda for session

### **Programmatic oversight of U10AA025286**

- Progress reports
- Information/description of MACH study on the NIAAA website

### **Clinicaltrials.gov records - <https://clinicaltrials.gov/ct2/show/NCT03169530>**

- Summary of changes to the clinicaltrials.gov record
- Clinical trial protocol

### **Papers published citing the grant for the MACH trial:**

[Moderate Alcohol Consumption and Chronic Disease: The Case for a Long-Term Trial. Alcoholism, clinical and experimental research. 2016 Nov; 40 \(11\) :2283-2291](#)

### **Other projects related to MACH trial**

#### **2014 Planning grant - [U34 AA023258 01](#)**

- Description and application
- Progress reports
- FOA submitted to <https://grants.nih.gov/grants/guide/pa-files/PA-11-169.html> and
- NIAAA sign on: <https://grants.nih.gov/grants/guide/notice-files/NOT-AA-13-004.html>
- Peer review meeting roster/list of applications reviewed

#### **2017 conference grant related to MACH [R13 AA025838](#)**

- Description of R13 conference grant
- Application for R13 conference grant
- Peer review meeting roster/list of applications reviewed

#### **2014 Conference grant [U13 AA023452](#)**

- Description of U13 conference grant
- Application for U13 conference grant
- Peer review meeting roster/list of applications reviewed

### **Other funding to lead PI:**

- Excel file from RePORT with all funding to lead PI

### **NIAAA portfolio and strategic planning**

Key topics funded by NIAAA (to compare 2008, 2012, 2017)

NIAAA Strategic Plans

Portfolio analyses by Office of Portfolio Analysis, Office of Extramural Research, Office of Science Policy



## Appendix item D: Timeline of events

### Key dates/timeline

#### 2013

- Throughout 2013, several sets of email correspondence and meetings involving NIAAA Staff, extramural investigators, and alcohol industry groups.
- June 9, 2013: email correspondences on which funding mechanisms and activity codes could be used to support the multi-site clinical trial, eventual PI of MACH trial included on correspondence
- June 14, 2013: NIAAA staff discussions about a business plan describing a moderate drinking clinical trial to share with Diageo
- June 30, 2013: NIAAA staff discussions of expediting U34 funding opportunity announcement
- July 12, 2013: Notice of NIAAA sign-on to NIAMS clinical trial planning grant FOA published
- July 23, 2013: email exchange between two NIAAA staff members discussing plans for travel on their “personal time” to Boston to meet with a U34 applicant
- September 20, 2013: NIAAA staff email discussion of draft legislative language to share with industry representatives and research society
- November 1, 2013: Application for U34 “Planning Grant for a Multi Center RCT of Moderate Alcohol Use on Chronic Disease” received
- December 12, 2013: Application for conference grant on “Interventional and Feeding Studies of Alcohol” received

#### 2014

- January 7, 2014: U13 conference grant and U34 planning grant reviewed
- February 14, 2014: U13 conference grant - “Interventional and Feeding Studies of Alcohol” - notice of award sent
- February 26, 2014: Meeting in Palm Beach, Florida at the Breakers - NIAAA staff member, extramural investigators, and industry representatives in attendance
- March 20, 2014: U34 planning grant “Planning Grant for a Multi Center RCT of Moderate Alcohol Use on Chronic Disease” notice of award sent.
- June 21, 2014: As per the U13 final progress report, the U13-supported meeting took place June 21, 2014 at the Hyatt Regency Bellevue in conjunction with the annual Research Society on Alcoholism Meeting. As per the progress report submitted by the PI, the meeting was “open to the public and attended by a wide variety of personnel, including NIAAA staff, public health professionals, alcohol industry members, and scientists in related fields.”
- November 18-20, 2014: Multiple emails discussing/planning a December 8 call on clinical trial protocol, inviting members of multiple companies (Inbev, Suntory, Sabmiller, Pernod-Ricard, Molson-Coors, Heineken, more) as well as NIAAA staff and eventual PI of MACH study
- December 11, 2014: Significant Item encouraging Randomized Controlled Trial - Congressional Record, p.H9833, Joint Explanatory statement on 2015 Approps Act/Significant Item:

“Moderate Drinking.--Numerous epidemiological and basic science studies have demonstrated that moderate drinking can be beneficial to health by reducing risk for coronary artery disease, type 2 diabetes, and rheumatoid arthritis, among others. However, these studies used different protocols or questionnaires, and may be difficult to compare. The agreement encourages NIAAA to undertake a multicenter, multiyear clinical study to clarify the health impact of moderate alcohol consumption.” Similar statement directed to CDC at p. H9830.

## 2015

- February 20, 2015: FNIH form for “request for collaboration” dated February 20.
- July 6, 2015: Letter approving that FNIH will work with NIAAA and external funders to support a multi-site clinical trial of health effects of moderate drinking
- October 5, 2015: Funding opportunity PAR-16-363 “Multi-Site Randomized Controlled Clinical Trial Research Center on Alcohol's Health Effects” published
- December 12, 2015: Earliest submission date for PAR-16-363
- December 18, 2015: Application to PAR-16-363 submitted by eventual PI of MACH trial

## 2016

- January 12, 2016: Close date of funding opportunity PAR-16-363
- March 29, 2016: Special Emphasis Panel Peer review for PAR-16-363
- April 19, 2016: Advisory Council Teleconference review of Moderate Alcohol and Cardiovascular Health Trial
- September 16, 2016: FNIH MOU signed
- September 30, 2016: Moderate Alcohol Cardiovascular Health Trial U10 cooperative agreement made

## 2017

- May 11, 2017: R13 conference grant “Symposium On The Health Effects Of Moderate Alcohol” awarded

## 2018

- February 5, 2018 – Trial begins enrollment
- May 10, 2018 – Trial enrollment is suspended

## Appendix item E: Emails reviewed by working group

### **SECTION (a):**

NIAAA staff interactions with industry to gain support of a multi-site clinical trial of moderate alcohol drinking health effects on cardiovascular health.

### **SECTION (b):**

Key documents related to funding opportunity development and application process

### **SECTION (c):**

Emails on summary statement response discussion between NIAAA program staff and PI, and on Council review

### **SECTION (d):**

Industry representative and NIAAA staff communication related to scientific planning/results of the study

## **SECTION (a):**

NIAAA staff interactions with industry to gain support of a multi-site clinical trial of moderate alcohol drinking health effects on cardiovascular health.

Direct interactions with alcohol industry groups, including: DIAGEO (multinational alcoholic beverages company), Anheuser Busch, DISCUS (Distilled Spirits Council of the United States)

Examples in section (a) include:

- June 14, 2013 emails
  - NIAAA senior staff discussion of business plan
- March 2014 emails: FNIH communications office asking NIAAA communications office about a wine industry blog that says that FNIH is initiating a search for industry money
  - NIAAA communications office shares blog post with an NIAAA division director who asks, "... Anything seem broken here?"
  - Thread is forwarded to NIAAA senior staff member
  - NIAAA senior staff member tells NIAAA communications office there has been no engagement with FNIH or industry
  - In a separate email thread, NIAAA senior staff member asks another, "Any desire to communicate anything to [an NIAAA division director]?"
    - Reply to this is "Best not to respond right now but we can't keep him totally in the dark."
- December 2014 conference call to discuss the trial with industry representatives, NIAAA staff and future PIs of MACH trial in attendance

(more examples in section (d))

**From:** [REDACTED]  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: COMMENTS/EDITING, please  
**Date:** Friday, June 14, 2013 2:18:11 PM

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Great—thanks. I’m happy to help try to add some language. But you get the idea—“we have a great proposal but can’t afford in this budget climate.....”

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 2:01 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: COMMENTS/EDITING, please

Right; as I said, alternative C will need major revision (and possibly total elimination... I don't have a copy with me; I'm at the DGAC meeting, without my laptop)

sent via BlackBerry

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 01:53 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: COMMENTS/EDITING, please

[REDACTED], as I’ve raised, I don’t see how we can include Alternative C, at all, without the appearance that we’re (A) soliciting funding, which we’re not allowed to do, and (B) specifically soliciting it from industry. We just flat out can’t come out and say that.

I don’t know how we could partner with the FNIH to perhaps allow THEM to undertake such an effort, but I can’t support that language as written. It’s not just a red flag, it’s a screaming red flashing neon light.

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Thursday, June 13, 2013 5:00 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** COMMENTS/EDITING, please

If you haven’t yet begun looking at the draft I sent earlier, use this one instead; if you have begun, this is the same, except that it now includes “Alternative C”, i.e., the one we actually want, so look at that section from this version.

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***MODERATE DRINKING RCT***  
***BUSINESS CASE***

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Version Number: 1.1  
Version Date: 06/13/13

## VERSION HISTORY

Version Number	Implemented By	Revision Date	Approved By	Approval Date	Description of Change
1.0	█	06/11/13			First draft
1.1	█	06/13/13			Added section 3.3

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## EXECUTIVE SUMMARY

*[Provide a synopsis of the key points of this Business Case document. Outline for the reader what the investment/project (hereafter referred to as "project") is about, what benefits it will provide, how it aligns with the goals and objectives of the organization, etc. Avoid ambiguous acronyms, terminology, concepts, etc.]*

**1. INTRODUCTION**

**1.1 PURPOSE OF BUSINESS CASE**

This Moderate Drinking RCT business case is provided to the NIAAA Director, and the Research Strategies Committee, for Concept Review of a proposed U34/U10 FOA.

**2. GENERAL PROJECT INFORMATION**

<b>Submission Date</b>	06/11/13
<b>Requested By</b>	[REDACTED]
	[REDACTED]
<b>Project Name</b>	Moderate Drinking RCT
<b>Desired Start Date</b>	FY2014

**2.1 PROJECT DESCRIPTION**

**Business Need**

For at least 15 years, consistent evidence (prospective epidemiological studies; small scale clinical feeding trials; animal studies on mechanisms and pathways; meta-analyses) has demonstrated that moderate drinking, generally defined as 1-2 servings daily of any alcoholic beverage, lowers one's cardiovascular, metabolic (e.g., type 2 diabetes; metabolic syndrome), and neurodegenerative (e.g., Alzheimers and other dementias) disease risk. A similar lowered risk for overall mortality highlights the prevalence of these diseases in modern populations by demonstrating that the benefit is not negated even by the potential increases in risk for specific cancers or other illnesses/injuries.

Nonetheless, with the exception of the recent (and unheralded) NINDS statement on a daily drink for stroke prevention, no government public health entity or scientific/medical professional society has been willing to recommend that patients specifically be advised to consider using alcohol as a risk-reduction intervention, in the way that physicians now often direct the use of low-dose aspirin. While many (e.g., U.S. Dietary Guidelines; American Diabetes Association) are willing to state that most individuals – including diagnosed patients – who currently drink at a moderate level need not be dissuaded from doing so, there remains a hesitance to be more proactive in the recommendation without a large-scale fully randomized clinical trial (RCT). Barriers to running such an RCT have been significant. However, we believe that the numerous frequently mentioned ethics, design, and process/procedural issues are resolvable with careful, well-monitored protocol planning and implementation. The more difficult issue is financial, as the RCT would only be useful if it (1) covered an extended timeframe, as opposed to the typical 6-weeks to 3-months feeding studies; and (2) had a large number of participants at multiple sites, thus allowing analyses of varying ethnic/genetic profiles; different beverage types; and different disease conditions (i.e., CVD; metabolic; neurodegenerative; combinations thereof).

**Goals/Scope**

We propose that NIAAA sponsor a 3-to-5 year multi-national RCT to determine the effects of physician-recommended daily alcohol consumption for individuals at risk for cardiovascular disease, type-2 diabetes, or Alzheimers onset. The FOA for this project would utilize the U10 mechanism, enabling the substantial involvement of NIAAA staff (specifically, [REDACTED] in the protocol. The consortium would include PIs/sites from the U.S., Europe, Asia, the

Middle East, and possibly Africa, as well as representation on the steering committee from WHO and/or OECD. The U10 would be preceded by a U34 FOA to design the protocol in detail.

Intended enrollees would be adults between the approximate ages of 40 and 60, who are at risk for, but not yet diagnosed with, any of the three conditions mentioned above (singly or in combination). The "at risk" determination would be physician-determined, based on standard physiological measures (e.g., cholesterol & blood pressure measurements, fasting glucose levels, etc.), genetic profiles where available/plausible, and family history information. Appropriate exclusions would be made (e.g., personal or family history of alcoholism; current medication profile that prohibits combination with alcohol; personal or family history of breast/ovarian cancer or oral/esophageal cancer, etc.).

The tested intervention would be physician advice to consume one serving of alcohol per day. No alcohol would actually be provided; however, system of vouchers to enable participants to obtain the alcoholic beverage of their choice (i.e., beer, wine, or spirits) at legitimate outlets will be implemented. Frequent monitoring of actual consumption levels and the various physiological measures relevant to the diseases under study will be undertaken throughout the entire length of the study. Regular screening for alcohol misuse will also occur throughout the study, with appropriate interventions in place when/if needed.

Analyses would address the following areas:

- (1) Level of adherence to physician advice
- (2) Changes in risk for each of the 3 disease situations (plus combinations thereof) based on daily drinking
  - a. If monitoring uncovers a gradient of adherence (i.e., substantial number of participants 'slipping' to a lesser amount, such as an average of 3-4 drinks/week; others averaging 2-3 per day), a more point-specific analysis will be undertaken
  - b. Differences between males and females
  - c. Differences between the various beverage types (we expect that, depending on the country, distinct groups of people will choose a particular beverage type with regularity)
    - i. Where possible, given the cultural constraints of item "c", differences between ethnic/racial (i.e., genetic) groups will be analyzed. Alternatively, it may be possible to type all participants for their alcohol-metabolizing genes, which are where we would expect the differences in health risk/benefit to reside.
- (3) Analysis of impacts to other health/disease areas (e.g., percentage who required early intervention or removal from study to prevent alcohol abuse problems; any changes in cancer or liver disease risk profiles; etc.)

The proposed project aligns with NIAAA's objectives to study the health effects of alcohol consumption, and the greater NIH/HHS objective of improving public health overall. According to the most recent CDC data [http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61\\_04.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf), heart disease is the #1 cause of adult mortality in the U.S. (stroke, Alzheimers disease, and diabetes -- all of which will also be assessed in this study -- are # 4, 6, and 7, respectively). We believe that this study has the ability to conclusively demonstrate whether daily moderate alcohol use, implemented solely through the practical and simple intervention of physician advice, to the group of patients medically determined to be at high risk for these diseases and simultaneously at lower risk for the potential consequences of alcohol use, can provide a positive change in the public's health.

## Risks/Issues

We believe that the protocol design (e.g., selection of participants past the age of risk for early-onset alcoholism; regular monitoring for both general health impacts and for potential alcohol abuse;

extensive involvement by NIAAA staff to ensure shut-down if necessary; provision of vouchers to discourage consumption of "back-alley"/"black market" risky beverages) lessens the risk of this RCT. At the same time, it is ONLY via a RCT that the implications of daily moderate drinking can be determined in a manner that meets the gold standard for medical advice; failure to undertake this study simply continues the already decades-long controversy where a large body of evidence remains suspect because it lacks the key imprimatur of an RCT.

An additional risk to NIAAA (and to NIH) is the possibility that this could become a tabloid-press issue, the sort of research topic that inspires some members of Congress, or certain agenda-based organizations, to unleash negative publicity by characterizing the study in sound-bites as a "multi-million dollar campaign to get people drunk". To counteract this, it is extremely important to precede the effort with an NIAAA- (and ideally, NIH-) approved scientific paper that lays out the knowledge to date which serves as the background for this initiative [i.e., the "Moderate Drinking update" paper currently under development]

Of course, the most significant "non risk-related" issue is the cost, particularly in this time of significant cutbacks to funding for biomedical research. Many will argue that there are far more pressing needs (e.g., treatment and prevention of alcohol mis-use) for the limited funds available, rather than a study that may eventually encourage more people to drink.

### 3. ALTERNATIVES AND ANALYSIS

#### 3.1 ALTERNATIVE A

Update the "Moderate Drinking" paper in the format of addressing the Hill Criteria (i.e., argument for 'causality' used in epidemiological research, in situations where RCTs are not feasible); persuade NIH to issue a formal recommendation advocating the daily consumption of alcohol as a prevention measure for CVD/diabetes/Alzheimers.

Pros:

- Paper is underway and will address those issues in any case
- No financial commitment necessary
- No time constraints (i.e., no need to wait for RCT completion and analysis of data)

Cons:

- Convincing NIH to take a controversial stand in the absence of RCT data will be difficult.
- May be objections (with or without countering data) from other ICs, or other HHS agencies (e.g., CDC)
- May be insufficient for acceptance by medical community, who would 'absorb' the risk of actually advising their patients without hard RCT data.
- The number and size of the various studies (whether small-scale feeding studies or large scale prospective epi studies), while establishing a general result, are inadequate to fully clarify the nuances (type of beverage vs. specific disease vs. population genetics, etc.)

#### 3.2 ALTERNATIVE B

Initiate an NIAAA-sponsored FOA to establish a multi-year, international multi-site RCT in line with the "Goals/Scope" section above, funded via a set-aside from each year's Congressionally-appropriated funds. With a target enrollment of 3,000 to 5,000 subjects per site, and a minimum of 5 sites, all operating for timeframe of 3 to 5 years (plus one planning year – U34, 1 start-up year, and 2 years for data analysis/reporting, projected costs are likely to be in the range of \$50 - \$80 million for the full project life (total of 7 to 9 years), or approximately a \$10 million-per-year commitment of funds.

Pros:

- Public health needs will be served by providing a scientifically justifiable answer to a controversial issue that relates to a number of the top causes of adult mortality
- Although "alcohol" is the topic that links all study participants, the disease outcomes being studied might encourage other ICs (specifically, NHLBI, NIDDK, NIA, and NINDS) to co-fund the project with NIAAA, reducing the impact to our overall budget.

Cons:

- A long-term commitment of appropriated funds is risky in the current budget atmosphere, where even today's tight fiscal climate could seem generous in comparison to what may lie ahead.
- Sharing the cost with other ICs will undoubtedly mean sharing control (protocol design decisions, staff involvement in a U mechanism, ultimate selection of consortium members and sites) with them as well. This may result in the inclusion of too many extraneous items (e.g., to answer additional, not necessarily related questions that are of interest solely to the other ICs) that make the protocol cumbersome for the subjects, causing retention problems; compromises that result in the alcohol questions not being adequately answered (e.g., a preference by the other ICs to only address red wine/antioxidants/polyphenols); etc.
- Dependence on the annually appropriated funds opens the risk of specific prohibitions for their use on this project in the out-years, in response to flare-ups of negative publicity by individual congresspersons or organizations, as described in the "Risks/Issues" section above.

### 3.3 ALTERNATIVE C

Secure funding from an outside source to pay for an NIAAA-sponsored FOA to establish a multi-year, international multi-site U-mechanism RCT in line with the "Goals/Scope" section above.

The ideal source of these funds would be a donation from the alcoholic beverage industry, whether via one or more companies making a direct gift, or a "bundling" effort coordinated by the industry trade associations (i.e., DISCUS, the Beer Institute, the Wine Institute, the Brewers Association, etc.), to the NIAAA Gift Fund or to the Foundation for NIH. While the donor(s) could – and should, for their own protection – specify that the money be used only for NIAAA grants, and maybe even specifically "for research on the health effects of moderate drinking" or "RCT to study the health effects of daily moderate drinking" (especially if the donation is made to FNIH rather than to the NIAAA Fund), that would be the only extent of their involvement and input. All aspects of study design, duration, proposal review, PI selection, data collection and analysis, and publication of results would be solely under the control of NIAAA and/or the consortium PIs (and any other agencies, such as WHO, that NIAAA chose to involve). In particular, the study is intended to assess the role of alcohol across various beverage types; therefore, we will NOT limit it to a particular type, even if all or most of the funding comes from that particular industry subgroup.

In the subsequent publication of findings (and in any disclosures that PIs need to make), all attribution of funding would be to NIH grants, not to the source of where any of the monies in grant pool may have originated. [No such reference is made to any other donors whose money might be part of some grant's funding; i.e., a grantee would normally cite "AAxxxxxx-01", not "money which came to NIH from the estate proceeds of Person X"]. As for accepting and publicly acknowledging the initial gift, there is a 2012 precedent for a similar high-dollar donation to NIH, by an industry that likewise wanted the funds used specifically to investigate issues of interest to them. [<http://www.washingtonpost.com/blogs/football-insider/wp/2012/09/05/nfl-donating-30-million-to-nih-for-brain-injury-research/>]. The guiding principle is that the donor is simply providing money to advance scientific research, and after that, steps away from the process completely; it becomes solely an NIH/NIAAA-managed research venture.

Once the data are released into the public domain via publication, the industry can use that information to make or bolster whatever arguments and claims they choose, as can any other person or entity who accesses the information. They may wish to use it generically to demonstrate their commitment to socially responsible activities; they may wish to use certain findings for their own marketing purposes; or they may choose to dispute findings that do not support their agenda – a use that will be met with more credence if they can at the same time point out that they were not “responsible” for any design flaws or data interpretations that they want to dispute. At that point, NIAAA and NIH are out of the process, other than to defend the research (or not) as they would for any other NIH-funded study.

We expect that the beverage industry would understand and accept this constraint, as they will be well aware (from recent issues over researchers who get grants directly from industry foundations such as ABMRF, and probably from even a brief glance at the responses to studies funded directly by pharmaceutical companies) that any hint of potential industry influence in the outcome makes that outcome less likely to be accepted by some (frequently vocal) segment of the public and/or the scientific and medical community.

Pros:

- Sufficient funding to ensure a well-designed, well-run RCT of a size and length to provide definitive data
- Full “firewall” between industry funding and NIH study management would defuse criticism of bias that an equivalent study with direct industry funding, or via an industry-designed entity (e.g., ABMRF) would spark
- Public health needs will be served by providing a scientifically justifiable answer to a controversial issue that relates to a number of the top causes of adult mortality

Cons:

- May be some initial negative publicity (innuendo) about perceptions that industry will now have influence on NIH activities and/or on HHS policy decisions in exchange for this donation
- Relatedly, may be increased congressional oversight demands on NIH to monitor these perceived ties.
- Industry may be unwilling to make the substantial dollar commitment
  - In general, or
  - While foregoing any input to or control of the resulting research protocol, or
  - Given that there is no guarantee that the results will support a conclusion that would benefit the industry (either in whole – i.e., benefit of alcohol; or in part, i.e., may find it only applies to certain beverage types or in very limited conditions/individual characteristics)

## 4. PREFERRED SOLUTION

### 4.1 PRELIMINARY STRATEGY/PLAN

### 4.2 FINANCIAL CONSIDERATIONS

*[Identify funding sources for all project component costs for the preferred solution. This should include consideration of items such as capital costs, operating costs, total cost of ownership, impact on other projects, funding requirements, etc.]*

### **4.3 PRELIMINARY WORK BREAKDOWN STRUCTURE**

*[Include a Work Breakdown Structure (WBS) for the preferred solution. The WBS organizes and defines 100% of the scope of project work to be accomplished and displays it in a way that relates work elements to each other and to the project's goals.]*

### **4.4 ASSUMPTIONS AND CONSTRAINTS**

*[Include a detailed explanation of any assumptions and/or constraints applied to the information documented within this business case.]*

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: URGENT - Can I do this?  
**Date:** Friday, June 14, 2013 2:37:00 PM

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Cardiovascular Health Effects of Ethanol Research Study

sent via BlackBerry

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 02:35 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: URGENT - Can I do this?

I really did not see that. But we still might need [REDACTED] to spell out what CHEERS stands for

“Clinical Health Effects of Ethanol Randomized Study”? Or did you already do that?

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 2:33 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: URGENT - Can I do this?

Don't you read your email? [REDACTED] and I are going with "CHEERS". And it will be a new drinking game; everytime you hear it, you must assume its a toast, and so have a drink.

sent via BlackBerry

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 02:27 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: URGENT - Can I do this?

That reminds me – we need to consult with [REDACTED] to come up with the right acronym for this project if it ever happens. Add him to the budget ☺

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 2:26 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: URGENT - Can I do this?

Okay. And weirdly enough, in theory we COULD afford it; considering the time span, it would be about \$8 - 10 million a year, which [REDACTED] was able to "find" when we were looking at CRAN numbers. Of course, we couldn't do much else, and this is hardly the most pressing NIAAA issue (NHLBI, maybe, but they won't go there), so its not going to happen -- but it "could".

sent via BlackBerry

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 02:18 PM



**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: URGENT - Can I do this?

I think discussing the study concept with [REDACTED] would be good. If it gets to a "there's no way we can pay for this," then just say it's worth development in case our budget circumstances change one way or another.....

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 2:08 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Fw: URGENT - Can I do this?

So, in that case, do you think I should at least discuss the study concept proposal with [REDACTED] at this point ?

sent via BlackBerry

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 01:58 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: URGENT - Can I do this?

Okay, I can do that.

sent via BlackBerry

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 01:50 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: URGENT - Can I do this?

If you are to share the parameters of the study, the ONLY thing I would say is that NIAAA currently doesn't have the funding level necessary to move forward with it. I wouldn't under any circumstance indicate that we're looking for, in need of, or in any other way seeking or hoping for an outside source. We absolutely can't look like we reached out to industry to seek funding.

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 1:33 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: URGENT - Can I do this?  
**Importance:** High

The concern is not about "NIH backing", it's that -- as a business -- they need something to describe what the "product" (i.e., the general proposed study) is, before they decide if its something they find it worth investing in. There are many things NIAAA studies; some of which the industry has zero interest in funding ([REDACTED]'s work); others of which they already contribute to through other avenues (underage drinking); others of which they likely see as something that should be paid for by a different industry, who would be more likely to benefit by a possible success (for example, Pharma).

There is no legitimate "business justification" to donate money at anywhere near this level, without some sort of proposal and rationale for the intended study itself; the people making the decision are answerable to their stockholders -- they can't just toss over this kind of money for a nebulous "proposal to be named later", even if it comes with stipulation that it must be used to study the effects of moderate drinking. (That could very easily be "interpreted" as an FAS study, a DUI study, an underage drinking study -- I personally could design any of those while still holding to the "moderate drinking" requirement).

In other words, the timeline of "first they donate a huge amount of money, then we draft a proposal of what to do with it" is not realistic.

It doesn't seem "unallowed" to send them the concept proposal without reference to industry specifically as the source of funds (if I am presenting it to, say RSA, as a "here's what NIAAA would love to do", I would still be including cost estimates, and yet not identifying a source, beyond saying it would have to come from outside funding/donations, since current budget issues make that source impossible, so there is certainly a rationale for such a document beyond only directly soliciting funds).

In something [REDACTED] sent us in October 2010 (not clear why; my suspicion is that it was prompted by the September 2010 SMRB decision -- and at the time, I actually filed it in my SMRB folder !), it specified:

#### GUIDANCE FOR COMMUNICATIONS WITH INDUSTRY AND OTHER EXTERNAL STAKEHOLDERS

- Officials may discuss general information about agency needs and future requirements

everything else in that memo seemed to relate to offering contracts, procurement deals, or soliciting employment...or letting them influence policy decisions....(the latter being why I think he sent it)

The need for this specific study is an "agency need"; that's the whole point I'm making in the business case document. The estimated cost (without naming a source, which WOULD be a direct request) is a "future requirement", and is "general information" in that it is simply an overall estimate (no details) and would be something I could provide to anyone -- if the press were to ask me, in relation to moderate drinking, that is the same info I would give them. So we are following [REDACTED]'s direction here.

sent via BlackBerry

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 12:08 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: URGENT - Can I do this?

I really am very concerned about anything being presented to industry from NIAAA directly. That could constitute "solicitation" of a gift, which we absolutely cannot do. The best timeline for something like this would be for the gift to come to F-NIH with interest in a study in this area of research from which we would "draft a proposal" in response. If they are concerned about having NIH backing, by giving it to the Foundation, that worry should be alleviated. We have to be very careful not to be seen as driving this process.

-----Original Message-----

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, June 14, 2013 11:57 AM Eastern Standard Time  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** URGENT - Can I do this?

[REDACTED]  
When we discussed this briefly after the senior staff meeting this week, you said the best way to get a sense of industry's interest in this was to have an extramural researcher make the approach.

Much to my surprise (as I told you I didn't think [REDACTED] or [REDACTED] could/would, and [REDACTED] had seemed even more skittish than [REDACTED] when we were discussing writing papers in collaboration with the BI), [REDACTED] @ harvard (who works with [REDACTED], and who thus will be part of the project) has done this ! In response, industry has requested a written document (preferably from NIAAA, whom they would rather deal with, instead of directly with any of the potential actual researchers). The turnaround time for this request is apparently "immediate", as they want to discuss it at a Board Meeting next week.

Assuming I can get my "draft business plan" into a non-draft state over the weekend, can I send it to them ? And, if so, would I need to run it by [REDACTED] first?

sent via BlackBerry

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED]@diageo.com  
**Subject:** Clinical Trials and Moderate Drinking  
**Date:** Tuesday, August 13, 2013 3:29:54 PM

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Dear [REDACTED]

I have been in touch with [REDACTED] and just wanted to thank you for the efforts you have made on our behalf. We believe, in the interest of timing, we need to proceed with alternative research plans. If you like to receive updates you could contact [REDACTED] who is overseeing the project.

Best

[REDACTED]

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** FW: Funding update  
**Date:** Monday, April 02, 2018 4:25:26 PM

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, December 18, 2017 3:21 PM  
**To:** [REDACTED] (NIH/NIAAA) [E] [REDACTED]@willco.niaaa.nih.gov>  
**Subject:** FW: Funding update

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Tuesday, August 13, 2013 3:02 PM  
**To:** [REDACTED] (NIH/NIAAA) [E] [REDACTED]@willco.niaaa.nih.gov>  
**Subject:** Re: Funding update

I spoke with [REDACTED]. Can you call me at [REDACTED]?

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Tuesday, August 13, 2013 02:46 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Funding update

He is trying to reach you --- have you gotten a voicemail?

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Tuesday, August 13, 2013 2:36 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: Funding update

Sounds good.

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Tuesday, August 13, 2013 02:08 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Funding update

Spoke with [REDACTED] and got advice on how to proceed with funding. He has instructed us to have [REDACTED] send an email to [REDACTED], "thanking her for her efforts, sorry it didn't work out, and saying that we are 'moving on'"; he says it is important to establish closure on this before taking the next step, and that it needs to come from [REDACTED] so that she understands that if she has any sort of 'still in the works' going on, she needs to let the Institute know that as an entity, not this semi-casual 'conversations between acquaintances whenever she gets around to it'.

[REDACTED] did tell [REDACTED] not to blindside you (since I told him you have been in contact with her, and she

may re-contact you to question the email), so [REDACTED] is supposed to give you a heads up before he sends it. On the other hand, we ([REDACTED] & I) are pushing him to send it today or tomorrow, so that I can take my next steps on Monday ([REDACTED] will be out soon for [REDACTED] and we need to take care of some pieces in the 'next steps' before he goes. In other words, at this point, "ASAP" is essential. So hopefully [REDACTED] will contact you today....

[REDACTED]

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**From:** [REDACTED] <[REDACTED]@discus.org>  
**Sent:** Thursday, November 14, 2013 6:01 PM  
**To:** [REDACTED] (NIH/NIAAA) [C]  
**Cc:** [REDACTED]  
**Subject:** Re: NIAAA-sponsored Clinical Trial of Moderate Drinking

[REDACTED], excellent, [REDACTED]

Sent from my iPad

On Nov 14, 2013, at 2:24 PM, "[REDACTED] (NIH/NIAAA) [E]" [REDACTED] [willco.niaaa.nih.gov](mailto:willco.niaaa.nih.gov)> wrote:

Dear [REDACTED],

As a follow up to my interim response, I can confirm that we are able to meet with you at DISCUS at 1:30 p.m. on Thursday November 21.

Looking forward to meeting with you.

Sincerely,

[REDACTED]  
National Institute on Alcohol Abuse and Alcoholism

**National Institutes of Health (NIH)**

5635 Fishers Lane, [REDACTED] Bethesda, MD 20892-[REDACTED]

Phone: [REDACTED]

Web: <http://www.niaaa.nih.gov>

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**From:** [REDACTED] [[mailto:\[REDACTED\]@discus.org](mailto:[REDACTED]@discus.org)]

**Sent:** Wednesday, November 13, 2013 3:17 PM

**To:** [REDACTED] (NIH/NIAAA) [E]

**Cc:** [REDACTED]

**Subject:** NIAAA-sponsored Clinical Trial of Moderate Drinking

[REDACTED]: Thank you for your phone call yesterday regarding a possible 10 year study on moderate drinking. While this sounds like an important and useful study, I have no idea whether or not industry funding could be developed to supplement government funding. In any case, we would be pleased to learn more about it. Unfortunately, we are already in the process of preparing for our next Executive Committee meeting so our schedule is a bit tight. Could you and your staff meet with us here at DISCUS at 1:30 p.m. on Thursday November 21? We would be pleased to listen to your brief and to have a full discussion about the planned study. Many thanks as always to you for thinking of us. Very best regards, [REDACTED]

**From:** [REDACTED]  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: Feedback from DISCUS  
**Date:** Friday, November 22, 2013 3:23:35 PM

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Again, congrats to [REDACTED] and the guys from Harvard and Yale (couldn't resist)

----- Original Message -----

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]; [REDACTED]  
**Sent:** Friday, November 22, 2013 2:54 PM  
**Subject:** Feedback from DISCUS

[REDACTED], [REDACTED], [REDACTED],

I had a phone call from [REDACTED] a few minutes ago. He wanted to tell me that he was tremendously enthused about the project and the presentation yesterday and wanted to thank us for being willing to come and make the presentation. He was very impressed with all 3 presenters. He stated that since the meeting he has only had the opportunity to talk with one company, who he said was a very large company in the spirits field though he declined to name it (as if we didn't know that it was Diagio since [REDACTED] was right there in the room and was with him the rest of the day) but he did point out that this big company was very enthusiastic as well. He stated that our group will likely need to make a presentation(s) to the other companies and very much wanted specifically the same two speakers (as he put it –“the guy from Yale and the guy from Harvard”). I assured him we could get the same team together (I hope that is true!) and we would be happy to come to a Board Meeting anywhere or meet with the companies individually anywhere they want to meet.

He then went on to hit on me again on our grant studying the effect of privatization on spirits and overall alcohol consumption. But today he did acknowledge that this is a battle between the brewers and vintners versus the distillers, so not everyone in the beverage industry is upset with transitioning from State control of spirits sales to privatization.

[REDACTED]



[REDACTED]

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Thursday, October 31, 2013 7:39 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: :)

I like what you guys came up with!

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Thursday, October 31, 2013 04:57 PM Eastern Standard Time  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: :)

No, he asked me if I was now going to contact her, or to wait for it to happen organically. I said I was NOT, since she has never responded to any of my previous attempts, and her last conversation on the topic was with [REDACTED], where SHE was going to get back to us (him) on September 10. So the ball is now totally in her court. He is going to tell her that specifically --- and we were debating the actual wording of the message ☺

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Thursday, October 31, 2013 4:54 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: :)

Is he anticipating needing to nudge her? Or has this been part of the strategy you 2 worked out all along? :)

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Thursday, October 31, 2013 04:29 PM Eastern Standard Time  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** :)

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**From:** [REDACTED] [hsph.harvard.edu](mailto:[REDACTED]@hsph.harvard.edu)  
**Sent:** Thursday, October 31, 2013 4:27 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE:

Dear [REDACTED] -  
Get your f\*cking as\* moving. Make check out to [REDACTED] @ NIAAA

Sound tactful?

[REDACTED]  
Associate Professor of Medicine  
Harvard Medical School

[REDACTED]  
Associate Professor of Epidemiology and Nutrition

[REDACTED]  
Harvard School of Public Health  
665 Huntington Av  
Boston MA 02115

[REDACTED] (fax)

From: [REDACTED] (NIH/NIAAA) [E]  
To: [REDACTED] (NIH/NIAAA) [E]  
Cc: [REDACTED] (NIH/NIAAA) [E]  
Subject: Re: story in today's news  
Date: Friday, February 28, 2014 7:15:32 PM  
Attachments: [image.png](#)

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The other thing is, this "Wine Industry Insight" appears to amount to no more than a blog as far as I can tell. The person who writes every article is also the founder. No one comments on any of the articles written, and I can't even tell how many subscribers this even has. It seems to be pretty worthless as far as a source of journalism is concerned. I don't even know whether there are sources or if he just makes things up.

I don't know what kind of response, if any, is necessary, but there is barely just enough accurate information that it hardly seems appropriate to dignify anything with a response.

[REDACTED]  
National Institute on Alcohol Abuse and Alcoholism  
[REDACTED] [Bethesda, MD 20892](#) [REDACTED]  
Phone: [REDACTED]  
Web: <http://www.niaaa.nih.gov>

On Feb 28, 2014, at 6:41 PM, "[REDACTED] (NIH/NIAAA) [E]"  
[REDACTED] [@mail.nih.gov](mailto:[REDACTED]@mail.nih.gov)> wrote:

[REDACTED],

[REDACTED] sent this to me since he is in South Dakota (I am in New Hampshire). I don't know what the appropriate response would be to this since there are many falsehoods in what is accessible with the part of the article we are allowed to read and we need a membership in order to see the full article. I guess I could fork out \$25 on my credit card to see what the whole article says.

We have not approached the FNIH concerning a moderate drinking study and we most certainly have NOT asked industry to fund a study. We have on our own funded a very small pilot study (R34 I believe) and an R13 conference grant to examine the feasibility of a clinical trial. We have no plans to engage in such a trial.

I don't know what is necessary in terms of a response or who should be engaged at this point in time.

[REDACTED]

[REDACTED]  
National Institute on Alcohol Abuse and Alcoholism  
[REDACTED] [Bethesda, MD 20892](#) [REDACTED]  
Phone: [REDACTED]  
Web: <http://www.niaaa.nih.gov>

Begin forwarded message:

**From:** "[REDACTED] (NIH/NIAAA) [E]"  
[REDACTED] <[willco.niaaa.nih.gov](mailto:willco.niaaa.nih.gov)>  
**Date:** February 28, 2014 at 5:03:50 PM EST  
**To:** "[REDACTED] (NIH/NIAAA) [E]"  
[REDACTED] <[@mail.nih.gov](mailto:@mail.nih.gov)>  
**Subject:** Fwd: story in today's news

Sent from my iPad

Begin forwarded message:

**From:** "[REDACTED] (NIH/NIAAA) [E]"  
[REDACTED] <[@niaaa.nih.gov](mailto:@niaaa.nih.gov)>  
**Date:** February 28, 2014 at 2:49:16 PM CST  
**To:** "[REDACTED] (NIH/NIAAA) [E]"  
[REDACTED] <[@willco.niaaa.nih.gov](mailto:@willco.niaaa.nih.gov)>  
**Subject:** FW: story in today's news

Hi, [REDACTED].

Do you know anything about the study described at this link?:

<http://wineindustryinsight.com/?p=52139>

[REDACTED] has not heard about this. Farther below, [REDACTED] at the Foundation of the NIH asks if we have any info.

Thanks, [REDACTED].

Best,

[REDACTED]

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, February 28, 2014 3:36 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: story in today's news

Hi [REDACTED],

I had not heard of this... but I would be very interested if you can find out more. Perhaps someone at FNIH?

**[REDACTED]**  
**Division of Metabolism and Health Effects**

National Institute on Alcohol Abuse and Alcoholism  
National Institutes of Health  
Bethesda MD 20892

Office Phone: [REDACTED]  
Cell Phone: [REDACTED]  
email: [REDACTED]@mail.nih.gov



**NIAAA ON THE WEB:**  
<http://www.niaaa.nih.gov>

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---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, February 28, 2014 2:17 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** FW: story in today's news

Hi, [REDACTED].

Re below, do you know anything about the study described at the link in [REDACTED]'s message?

Thanks,

[REDACTED]

---

**From:** [REDACTED]  
**Sent:** Friday, February 28, 2014 2:10 PM  
**To:** NIAAA Press Office  
**Subject:** story in today's news

Good afternoon.

I've just had a story in the publication Wine Industry Insight brought to my attention: <http://wineindustryinsight.com/?p=52139>

As you will see, the story refers to a large study for which the "NIH Foundation" is raising money from industry. This is a pretty odd story for a number of reasons, and no one here knows that it is referring to. I would be grateful if you might have any insight.

Thanks in advance.



Foundation for the National Institutes of Health  
9650 Rockville Pike | Bethesda, MD 20814 | [www.fnih.org](http://www.fnih.org)



<image003.jpg>

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NCATS) [E]  
**Subject:** RE: story in today's news  
**Date:** Monday, March 3, 2014 4:04:14 PM

---

O.K. We can decide if it is you or me or both who talk with him.

I did have a phone conversation with [REDACTED] from the Beer Institute today on some other issues like the Dietary Guidelines that they keep bugging us (me) on. She received a message from [REDACTED] that she had left NIAAA and she asked about the moderate drinking study and if it was still moving forward. I relayed that the desire for such a study is still in the long-term agenda of NIAAA but that many issues were still pending before it could be a reality. She asked if the conference in June at RSA on the issue was still on and I indicated yes.

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 3:58 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: story in today's news

I agree we can't, and with [REDACTED] having retired, we really need to place whatever future efforts we might undertake in a home—which I guess would most likely be DMHE. I'm happy to talk with him whenever you like.

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 3:56 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: story in today's news

[REDACTED]

Best not to respond right now but we can't keep him totally in the dark. I am more than happy to talk with him and convey an accurate picture of the eventual initiative we are interested in. If anything was sent now it would have to be just to emphasize that there are many inaccurate statements in the article.

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 3:22 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** FW: story in today's news

FYI. Any desire to communicate anything to [REDACTED]? I told him not to worry about responding to [REDACTED], as it's not his issue to deal with internally.

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 3:05 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]

**Subject:** FW: story in today's news

Hi, [REDACTED].

I sent the full article from Wine Industry Insight to [REDACTED].  
[REDACTED]'s response is below.

Any guidance re how best to respond?

Thanks,

[REDACTED]

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 2:57 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: story in today's news

So let me see if I understand this correctly, [REDACTED] without input from [REDACTED] or [REDACTED] or the DMHE has initiated this process? Anything seem broken here?

[REDACTED]

***Division of Metabolism and Health Effects***

National Institute on Alcohol Abuse and Alcoholism

National Institutes of Health

Bethesda MD 20892

Office Phone: [REDACTED]

Cell Phone: [REDACTED]

email: [REDACTED]@mail.nih.gov



NIAAA ON THE WEB:

<http://www.niaaa.nih.gov>

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 2:42 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: story in today's news

Hi, [REDACTED].

[REDACTED] at FNIH got access to the full story. It's pasted below.

Best,





US Govt Asking Industry To Fund Landmark Alcohol/Health Study The federal government, along with scientists from Yale and Harvard, are asking wine, beer and spirits organizations to fund most of a landmark clinical study on the health effects of moderate alcohol consumption.

According to documents provided to Wine Industry Insight, the National Institute of Alcohol Abuse and Alcoholism (part of the National Institutes of Health) plans to spend \$2 million to \$3 million on a six-year, multinational clinical trial that it estimates will cost \$6 million to \$9 million per year to complete.

The NIH Foundation is seeking outside funding which includes asking beer, spirits, wine, insurance and drug companies to come up with \$24 million to \$36 million towards an estimated \$36 million to \$54 million total cost.

Spirits: Hot On The Idea, Beer: Warm, Wine: Cool

Sources said that the Distilled Spirits Council of the United States (DISCUS) is among the early supporters of the study with beer being “very interested.” The same sources familiar with the process says wine industry interest has been “cool.”

The Wine Institute had not responded to WII’s query about this by publication deadline.

“Study To End All Studies” Aims To End Alcohol/Health Ambiguities

“This issue [moderate alcohol consumption and health] has floated around for decades, but there have never been the sort of clinical trials that are needed in order to make official recommendations on moderate drinking, “ said the informed source. “Those trials are vital but very expensive. This is the study that should be able to end the ambiguity once and for all. This is the study to end all studies.”

Study Would Provide Physician Recommendation For Patients

The source said that physicians have “besieged” government agencies to provide an official statement on moderate consumption because they need to know what to recommend.

DISCUS Taking The Program Seriously

“While there are risks in every new endeavor, this study will be a landmark piece of research that should legitimize moderate consumption,” said a member of the DISCUS board of directors, speaking off the record to Wine Industry Insight.

The source added that the only risk involved is that some new negative information might be

uncovered. “The evidence is overwhelming that moderate consumers live longer,” the source said. “The risk of discovering negative information is very small given the decades and billions that the government has spent trying to prove the French Paradox wrong.”

The source said that the DISCUS board was scheduled to take up the issue during its Feb. 27 meeting.

#### Looking For Equal Contributions From Wine, Beer and Spirits

The effort to raise funds has asked for \$1 million per year each from wine, beer and spirits.

The fundraising has been compared to the \$30 million that the National Football League granted to the NIH Foundation in 2012 for head injury and concussion research.

#### NIAAA Participant Was Top Author On Moderate Drinking Recommendations For U.S. Dietary Guidelines

The NIAAA’s chief proponent for the new proposed study is [REDACTED] Office of the NIAAA Director. She was the chief author of a pivotal study assessing the health effects of moderate alcohol consumption. The study was conducted as part of the 2006 update of the National Dietary Guidelines.

#### Yale & Harvard Profs Prominent In Their Fields

The prime movers from the university research sector are [REDACTED] of the Yale University School of Medicine and [REDACTED] of the Harvard University Medical School.

[REDACTED]

Dr. [REDACTED] serves as [REDACTED], Department of Psychiatry, and [REDACTED], Yale-New Haven Hospital.

He also serves as [REDACTED] NIAAA Center for the Translational Neuroscience of Alcoholism; [REDACTED] Clinical Neuroscience Division, VA National Center for PTSD; [REDACTED] VA Alcohol Research Center; [REDACTED] Schizophrenia Biological Research Center, DVA.

The following comes from Dr. [REDACTED]’s online biography: Dr. [REDACTED] is a leading expert in the areas of alcoholism, schizophrenia, and post-traumatic stress disorders. His work links psychopharmacology, neuroimaging, and molecular genetics to study the neurobiology and to develop novel treatments for these disorders.

He is a member of the Institute of Medicine of the National Academy of Sciences. He also serves in a variety of advisory and review capacities for NIAAA, NIMH, Wellcome Trust, Brain and Behavior Research Foundation, and the Karolinska Institutet.

He previously served on the National Alcohol Abuse and Alcoholism Advisory Council (NIAAA), the Department of Defense Psychological Health Advisory Committee, the NIMH Board of Scientific Counselors (chair, 2005-2007), and American College of Neuropsychopharmacology (president, 2012).

Dr. [REDACTED] also edits the journal, Biological Psychiatry (impact factor: 9.247).

[REDACTED]

Dr. [REDACTED] is an Associate Professor of Medicine and General Internist at Beth Israel Deaconess Medical Center.

The following comes from Dr. [REDACTED]'s online biography: Dr. [REDACTED]'s primary research interests are investigating the role of dietary and lifestyle factors - particularly alcohol consumption - on the incidence and prognosis of cardiovascular and neurovascular disease and its risk factors. As a general internist and clinical investigator, his research has incorporated ongoing epidemiological studies, utilized hospital-based clinical data, and interventional studies. The outcomes of this research have been broad-based and include diverse health effects of alcohol ranging from novel cardiovascular risk factors and subclinical vascular disease to falls and suicide. Recent work in collaboration with [REDACTED] of BIDMC's Cardiovascular Division and [REDACTED] of the Harvard School of Public Health seeks to examine novel biomarkers in important candidate pathways leading to cardiovascular disease and diabetes in large, ongoing cohort studies.

Between them, the two have authored more than 650 scientific papers, articles and reviews.

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 12:05 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: story in today's news

Hi [REDACTED],

The story appears to have originated in the Wine Executive News. Can we get a copy of the full story. It sounds like an FNIH initiative and not one that would have been initiated by NIAAA so I am not surprised that we are in the dark.

[REDACTED]

***Division of Metabolism and Health Effects***

National Institute on Alcohol Abuse and Alcoholism

National Institutes of Health

Bethesda MD 20892

Office Phone: [REDACTED]

Cell Phone: [REDACTED]  
email: [REDACTED]@mail.nih.gov



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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 10:09 AM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: story in today's news

Hi, [REDACTED].

I asked [REDACTED] and [REDACTED] about it, and [REDACTED] told me that there were no plans for such a trial at this time, which is what I passed along to the communications guy at FNIH.

I'll keep you posted when/if I learn more.

Best,

[REDACTED]

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, March 03, 2014 10:05 AM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: story in today's news

Hi [REDACTED],

Were you able to find anything more about the FNIH story?

[REDACTED]  
***Division of Metabolism and Health Effects***  
National Institute on Alcohol Abuse and Alcoholism  
National Institutes of Health  
Bethesda MD 20892  
Office Phone: [REDACTED]  
Cell Phone: [REDACTED]  
email: [REDACTED]@mail.nih.gov



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---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Friday, February 28, 2014 2:17 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** FW: story in today's news

Hi, [REDACTED].

Re below, do you know anything about the study described at the link in [REDACTED]'s message?

Thanks,

[REDACTED]

---

**From:** [REDACTED]  
**Sent:** Friday, February 28, 2014 2:10 PM  
**To:** NIAAA Press Office  
**Subject:** story in today's news

Good afternoon.

I've just had a story in the publication Wine Industry Insight brought to my attention:  
<http://wineindustryinsight.com/?p=52139>

As you will see, the story refers to a large study for which the "NIH Foundation" is raising money from industry. This is a pretty odd story for a number of reasons, and no one here knows that it is referring to. I would be grateful if you might have any insight.

Thanks in advance.

[REDACTED]

[REDACTED]  
Foundation for the National Institutes of Health  
9650 Rockville Pike | Bethesda, MD 20814 | [www.fnih.org](http://www.fnih.org)

**From:** [REDACTED] (NIH/NIAAA) [C]  
**To:** [REDACTED] @bidmc.harvard.edu; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Follow-up  
**Date:** Monday, August 4, 2014 4:04:14 PM  
**Attachments:** [image001.jpg](#)

---

[REDACTED],

O.K., I will talk with [REDACTED] and reach out again to [REDACTED]. Then let's see how it goes.

[REDACTED]

[REDACTED]  
National Institute on Alcohol Abuse and Alcoholism  
**National Institutes of Health (NIH)**  
5635 Fishers Lane, [REDACTED] Bethesda, MD 20892 [REDACTED]  
Phone: [REDACTED]  
Web: <http://www.niaaa.nih.gov>



---

**From:** [REDACTED] @bidmc.harvard.edu; [REDACTED] @bidmc.harvard.edu]  
**Sent:** Monday, August 04, 2014 4:01 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Follow-up

[REDACTED],

Thanks so much for your insight. As it turns out, our Russian contact came from [REDACTED], so I defer to her expertise (although [REDACTED] worked with [REDACTED], who also advocated for him)!

I don't know [REDACTED] at all – he was at MGH and I'm at BI (and Harvard people can be ridiculously parochial) – but hopefully the news proves to be good. I can only imagine how busy you were when you became [REDACTED], and I'm sure things must be equally busy at NINDS.

If [REDACTED] wants to reach out to [REDACTED] – or would like something from me – just let me know. I think that our chances with the brewers and distillers would only go up with buy-in from other sources, including wine, if we can find any.

With all best,

[REDACTED]

---

**From:** [REDACTED] (NIH/NIAAA) [E] [[mailto:\[REDACTED\]@willco.niaaa.nih.gov](mailto:[REDACTED]@willco.niaaa.nih.gov)]  
**Sent:** Monday, August 04, 2014 3:49 PM  
**To:** [REDACTED]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Follow-up

Dear [REDACTED],

This seems to be moving along well and I am pleased about that. As for the Carlsberg recommendations, I do like the idea of including Chinese and Danish sites, but I worry about Russia with past experience on access and data sharing. Further, the Russian drinking norms are so different that it could pose problems, but you are in a better position to judge that.

I will try to answer each of the questions you posed:

- (1) [REDACTED]: I have been lax in getting in contact with him but I will send him an email to try to set up a meeting of him (and any people from NINDS that he wants) and you. One new factor is that [REDACTED] is retiring [REDACTED] NINDS shortly (announced last week) and [REDACTED] will be [REDACTED]. This can be either good or bad – the good is that, from my knowledge of [REDACTED] it is likely that she would have been negative on any study related to the positive or negative effects of alcohol so having [REDACTED] in the leadership position could be a benefit; the negative is obvious is that he will be busier and harder to schedule a meeting with. I was also wondering how well you knew [REDACTED] – he came to NIH from Harvard around 2007?
- (2) I do think it is worth going after the large wine producers like Freixenet. However, I don't have any clear leads, maybe [REDACTED] does. One possibility is [REDACTED] [REDACTED] of the California Wine Institute and now [REDACTED] for the Gallo Research Center at UCSF. He has lots of wine contacts and may have for Europe too. [REDACTED] was very friendly with [REDACTED] at the Gallo Center meeting as if he wanted to help in some way.
- (3) As for timing of the money, the sooner the better, but also better late than never. [REDACTED] [REDACTED] is supportive of the study so we can start to move anytime we have funds. We could start as early as 2015 if funds were there, if not 2016 or even 2017 in my view.

Best wishes,

[REDACTED]

[REDACTED]  
National Institute on Alcohol Abuse and Alcoholism  
**National Institutes of Health (NIH)**  
[REDACTED], [REDACTED], Bethesda, MD 20892- [REDACTED]  
Phone: [REDACTED]  
Web: <http://www.niaaa.nih.gov>



---

From: [REDACTED] [@bidmc.harvard.edu](mailto:[REDACTED]@bidmc.harvard.edu) [mailto:[REDACTED]@bidmc.harvard.edu]

**Sent:** Monday, August 04, 2014 2:36 PM

**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]

**Subject:** Follow-up

[REDACTED] and [REDACTED],

I just wanted to give you a brief follow-up and think about next directions. As you know, the group of sponsors who belong to GAPG convened a group of four representatives ([REDACTED], Diageo; [REDACTED], DISCUS; [REDACTED], ABI; and [REDACTED], ICAP), who provided us with a list of questions and concerns. We replied to them last week and hope that we have addressed their primary concerns.

Carlsberg reached out to us separately to articulate some specific requests (specifically to add Chinese, Russian, and Danish sites) and to meet with the head of the foundation that owns the brewery. We have confirmed a date in late August for an afternoon and dinner meeting. I believe we can address their wishes very satisfactorily at that time.

In terms of next steps:

1. Is a meeting with [REDACTED] at NINDS still being considered? Is there anything I can do in that regard? It seems like a terrific strategy.
2. During our trip to Barcelona, I visited the Freixenet winery, which is clearly huge. It reminded me that we don't have any buy-in from the wine industry at all, but Freixenet at least would seem to be large enough to contribute at least modestly (100 million bottles per year or so). Is it worth exploring wine again? Do you have counterparts elsewhere who might approach larger foreign producers?
3. In terms of timing, I've been asked by industry when we need a firm commitment. Do you have a good sense for how to respond to that? Obviously, we'd love to have the timing work so that we start sometime in early-mid 2015 and don't lose any of our current momentum.

With best wishes (and hoping it's not too muggy there),

[REDACTED]

---

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**From:** [REDACTED]@bidmc.harvard.edu  
**To:** [REDACTED]@bidmc.harvard.edu; [REDACTED]@gmail.com; [REDACTED]@uea.ac.uk; [REDACTED]@juiusclinical.com; [REDACTED]@hsph.harvard.edu; [REDACTED]@lupui.edu; [REDACTED]@hsph.harvard.edu; [REDACTED]@hsph.harvard.edu; [REDACTED]@gmail.com; [REDACTED]@hsph.harvard.edu; [REDACTED]@tno.nl; [REDACTED]@wfubmc.edu; [REDACTED]@ucdavis.edu; [REDACTED]@kuhp.kyoto-u.ac.jp; [REDACTED]@jhmi.edu; [REDACTED]@clinic.ub.es; [REDACTED]@umcutrecht.nl; [REDACTED]@db3.so-net.ne.jp; [REDACTED]@nuns.edu.sg; [REDACTED]@uniklinik-ulm.de; [REDACTED]@wum.edu.pl; [REDACTED]@gmail.com; [REDACTED]@gmail.com; [REDACTED]@spb-gmu.ru; [REDACTED]wakehealth.edu; [REDACTED]@iecs.org.ar; [REDACTED]@gmail.com; [REDACTED]@hsph.harvard.edu; [REDACTED]@channing.harvard.edu; [REDACTED]@vip.sina.com; [REDACTED]@wakehealth.edu; [REDACTED]@nexs.ku.dk; [REDACTED]@nexs.ku.dk; [REDACTED](NIH/NIAAA) [E]; [REDACTED]@nku.hk; [REDACTED]@jhu.edu; [REDACTED]@channing.harvard.edu; [REDACTED]@mail.harvard.edu; [REDACTED]@yahoo.com; [REDACTED]@wakehealth.edu; [REDACTED]@juiusclinical.com

**Subject:** Reminder: Alcohol Trial Conference Call, Wed 12/10 at 7am EST  
**Date:** Tuesday, December 9, 2014 12:11:26 PM  
**Attachments:** [ICAP Call Minutes.docx](#)  
[DA Conference Call 12 5 14.docx](#)  
[RR Conference Call 12 2 14.docx](#)

---

Dear Colleagues,

We will be having our biweekly call tomorrow, 12/10 at 7am EST (See dial in numbers listed below).

We will be discussing the following items:

- 1) Recent call with ICAP
- 2) Recruitment and Retention (RR) Subcommittee recommendations
- 3) Design and Analysis (DA) Subcommittee discussion of outcomes

Attached is a summary of the conversation with ICAP and the latest call minutes for the RR\* and DA groups.

\*Note: The RR minutes doc includes information from two of our calls. It lists a discussion of original concerns, Ken's responding comments, and our resulting recommendations (in blue font).

Please feel free to contact me with any questions.

Call schedule moving forward

Wed 12/10 at 7am EST: RR and DA present

Wed 1/7 at 7am EST: IA and MPQC present

Wed 1/21 at 7am EST

Wed 2/4 at 7am EST

Wed 2/18 at 7am EST

Call in information:

Argentina Toll Free: 0800 666 0109

China, Beijing: +86 10 5667 0004 (not toll-free, local calling fees apply)

Denmark Toll Free: 80 70 35 95

Germany Toll Free: 0800 588 9165

Hong Kong Toll Free: 800 901 667

Japan Toll Free: 0120 840 900

Netherlands Toll Free: 0800 023 1432

Russia Toll Free: 8 800 500 9280

Singapore Toll Free: 800 616 3202

South Africa Toll Free: 0800 999 435

Spain Toll Free: 900 828 071

UK Toll Free: 0800 358 6403

US/Canada Toll-Free: 1-877-860-3058

For those of you who travel often, a more complete list of call in numbers can be found here:

<https://mtginfo.pgi.com/globalcallmanagement.asp?>

[wbebid=9820041&cid=da6ee6b4d7ed5a17d775fcee4d4d&confid=da67e6bbd7e65a1fd77cfce64d40&brandid=1](https://mtginfo.pgi.com/globalcallmanagement.asp?wbebid=9820041&cid=da6ee6b4d7ed5a17d775fcee4d4d&confid=da67e6bbd7e65a1fd77cfce64d40&brandid=1)

Host Passcode: [REDACTED]  
Guest Passcode: [REDACTED]

---

[REDACTED]  
Research Project Administrator  
Division of General Medicine and Primary Care Beth Israel Deaconess Medical Center  
1309 Beacon Street  
Brookline, MA 02446  
Tel: [REDACTED]

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# ICAP Call Minutes

Monday December 8th, 9am EST

Hosts – [REDACTED] and [REDACTED] of ICAP

Alcohol Trial group attendees – [REDACTED] [REDACTED] [REDACTED] [REDACTED]  
[REDACTED] and [REDACTED]

**Also attended by the industry leaders representing ABI, Suntory, and Heineken, among others**

## 1. RECAP FROM [REDACTED]

- **Previous Research** - For 30-40 years people who drink alcohol in moderation have a lower risk of developing heart attacks and DM. The problem (meaning the reason this has not lead to medical recommendations) with those studies is that they are entirely observational. There have also been small and intermediate term trials, where alcohol level is dictated by the investigator. These have gone from as short as a couple of weeks to a year in duration. None have looked at heart disease since they have been too short and small. This is not considered gold standard evidence to lead the health recommendations .
- **NIAAA** – Is a branch of NIH that funds the largest amount of alcohol related research in the world. It is for this reason the preeminent funder anywhere. Much of the research is concerned with addictions and problems related to alcohol intake.

They now want to investigate the relationship between alcohol intake and lowered cardiovascular and diabetes risk to see if it is casual. They have provided our team with two small planning grants which has allowed us to bring together a group of experts with whom we will work to determine how best to structure this project.

Should it secure funding, it will release RFA to conduct a large clinical trial. NIAAA would be a partner in helping to run the trial. meaning we will need to undergo all of the standard scientific review required for all federally funded research in the US.

- **What would a trial look like?** - It would be a randomized, multicenter, trial. Individuals interested in the trail will come the field centers and sign a consent form. They will be at high cardiovascular risk (so we can conduct this in a 5yr period). They would fall in an intermediate category of drinking a little, but less than daily. They would be randomized to not drink at all or to drink daily for 5 years.

We will provide support and monitoring to make sure they stay close to their assigned arm. It's ok if there is some decay, but we want to prevent this as much as possible. Over the course of their participation, we will monitor for primary and secondary outcomes and for safety outcomes.

Timeline - Each individual will be active in the study for 5 of the total 10yrs. There will be 6 months of ramp up. There will be a vanguard period, which means, for the first year, we will roll the trial out at a smaller number of sites and monitor recruitment rates. This gives us the opportunity to measure feasibility, and initiate course correction. (In a pilot study – you determine feasibility, but conclude and start the main study new, so all initial data is lost). There will be 3 years for enrollment, so the last person would finish the trail around year 8. The last two years are for data analysis and publication.

Making assumptions based on rates of the recruitment criteria and accounting for drop out and non-compliance, we will need to recruit 13,950. Ppts will come in every 6 months for biomarker measurement, and we will monitor hospitalizations. On a regular basis, we will administer (by web or phone), timeline follow back for alcohol consumption. We will also use GGT and HDL biomarkers to determine if the groups are different to the extent that we would expect. There will be compensation for ppts time and effort, and reimbursement for alcohol purchases.

External review board will monitor un-blinded data throughout the project to look for significant benefit/risk to the intervention and stop if in the best interest of the ppts.

Investigators on the team now, are the best people to help us build the protocol, and are not necessarily representative of all the sites we will involve. They have conducted very complex clinical trials to change diets or take combinations of various drugs.

## 2. QUESTIONS

- **ICAP, [REDACTED]** – Can you clarify the role of fNIH and NIAAA?

[REDACTED] – We plan to follow the normal NIH procedures for funding a clinical trial. We will release an RFA calling for the consortium to respond to the request for this trial, and it will be reviewed by an external scientific committee.

fNIH – Decides whether this is something that they would want to take on, and works with the funders to ensure that the contractual arrangements are mutually acceptable. When they acknowledge the funding, it will go to a NIAAA grant number. There may also be the opportunity to contribute fund directly to NIAAA.

- **ABI, [REDACTED]** – How does the vanguard model impact cost?

[REDACTED] – There are two advantages of this “scale up” model. 1) The primary outcome in the vanguard would be hitting recruitment goals and broadly seeing difference in biomarker between the two groups. If we don’t see convincing data then we stop the trial. The early years in a trial are usually more costly due to need to hire and build infrastructure, so the costs from launch through the vanguard would likely be similar to the yearly cost going forward. 2) This structure also allows course correction for the rate of of outcomes and its relationship to target recruitment numbers (ie. If the rate is higher we can adjust the total recruitment down and save \$/time).

█ - Also, each site will need to present their budget and justification at the outset of launch, and it will be reviewed/approved by NIAAA.

- **ICAP, █** – What is the anticipated timing of when it would come to NIAAA for review?

█ – It's likely that the funding opportunity will be released in early 2015, with the group funded by mid-late 2015.

- **ICAP, █** – Would you think that the CDC or someone else may pick up the idea and go a different way with it?

█ – Yes, we have been approached by different groups, and some of these groups have very different motives eg. investigating the relationships btwn alcohol and breast cancer.

█ – I am often defending the J shaped curve. Some people also want to prove there is no affect.

- **█, ?** – How will the monitoring and the screening work?

█ – Screening during the trial will occur every 6 months when we will measure information related to safety and outcome end points. In between visits, we will monitor for problems and encourage adherence by administering timeline follow-back. These will be proctored in the way that the ppts are asked trigger questions to help them recall relevant behavior . This practice is commonly used in alcohol addiction trials.

- **ABI, █** – What is the dissemination plan of releasing research results?

Ken – This will depend on what happens during the trial. There will be a 1yr ramp up, 2-3 years of enrollment, 5 years of active intervention, followed by 2 years of analysis and publication. The protocol would be the only initial publication, along with some smaller ancillary studies. From the beginning of the vanguard period through year 8, we could publish studies on the physiological outcomes related to alcohol intake. However, we wouldn't have access to the data to publish final results, until the last few years of the study.

- **ABI, █** Can you describe the data availability to be shared with other researchers? What happens to the blinded data after the study? And will there be any differentiation btwn wine, beer, and spirits?

█ – We will need to make data available a year after the study concludes, and we can do so in the form of controlled data sets.

The question we are asking is, “Does drinking one drink daily alter risk for heart disease and DM vs. not all?”, so we will not separately randomize ppts to different alcoholic beverages (partly bc we believe that giving the ppts this freedom of selection will help with compliance). However, since we will be recording what people are doing, we will be able to ask the question of whether

there is a difference between the groups who consume different types of alcohol. If we were to separately randomize to different groups the study would need to be much larger/longer.

██████████ Data would be deposited in a repository... (inaudible)

- **Suntory, ?** – Is the funding source going to impact the interpretation of the results by external agencies?

██████ – We will be running the study in conjunction with NIH/NIAAA who is the biggest source of data for the WHO. As long as that firewall is established between industry, and the design/management of the trial, it should remove doubt.

- **Suntory, ?** - Can you speak to the integrity of the self-reported data?

██████ – That is the standard for how we conduct all stage 3 clinical trials. We do not observe the ppt receive the intervention, but rely on them to follow instruction and use reporting tools to provide compliance data.

- **Suntory, ?** – Is the intention to publish results even if they are less desirable eg. negative or mixed?

██████ – Yes, however the peer review comments from the initial analysis of our study design were that we will most certainly see an impact for DM and we are not enrolling people of high risk for breast cancer.

██████ (ICAP) - ICAP in principle requires that there be publication regardless of the results.

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED]@bidmc.harvard.edu; [REDACTED] (NIH/NIAAA) [E]  
**Cc:** [REDACTED]@yale.edu  
**Subject:** RE: Moderate Alcohol Study  
**Date:** Thursday, March 20, 2014 2:14:00 PM

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Having [REDACTED] on board would be fine with me.

[REDACTED]

[REDACTED]  
National Institute on Alcohol Abuse and Alcoholism  
**National Institutes of Health (NIH)**  
[REDACTED], Bethesda, MD 20892- [REDACTED]  
Phone: [REDACTED]  
Web: <http://www.niaaa.nih.gov>



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**From:** [REDACTED]@bidmc.harvard.edu [REDACTED]@bidmc.harvard.edu]  
**Sent:** Thursday, March 20, 2014 2:06 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Cc:** [REDACTED]@yale.edu  
**Subject:** RE: Moderate Alcohol Study

Great news all around. May I cc [REDACTED] to join?

Sent from my Verizon Wireless 4G LTE smartphone

----- Original message -----

**From:** "[REDACTED]"  
**Date:** 03/20/2014 11:00 AM (GMT-08:00)  
**To:** "[REDACTED] (NIH/NIAAA) [E]" ; [REDACTED] (NIH/NIAAA) [E]"  
**Cc:** "[REDACTED]" ; [REDACTED]  
**Subject:** Re: Moderate Alcohol Study

Great! [REDACTED] from my shop has my schedule. [REDACTED]

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**From:** <[REDACTED] [E] (NIH/NIAAA)" <[REDACTED]@willco.niaaa.nih.gov>  
**Date:** Thursday, March 20, 2014 10:12 AM  
**To:** "[REDACTED] (NIH/NIAAA) [E]" <[REDACTED]@nih.gov>  
**Cc:** Yale University <[REDACTED]@yale.edu>, [REDACTED] <[REDACTED]@bidmc.harvard.edu>  
**Subject:** FW: Moderate Alcohol Study





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**From:** <[REDACTED] [E] (NIH/NIAAA)" <[REDACTED]@willco.niaaa.nih.gov>  
**Date:** Thursday, March 20, 2014 9:51 AM  
**To:** Yale University [REDACTED]@yale.edu>  
**Subject:** RE: Moderate Alcohol Study

Hi [REDACTED],

I do know that [REDACTED] is supportive of this study. The issue is setting up a meeting with DISCUS and Beer given [REDACTED]'s incredibly busy schedule right now. I know he does want to meet with the alcohol constituencies which we try to set up in the reasonable near future.

Based on the letter that [REDACTED] sent to you and [REDACTED] the key issue may be to get some international commitment before DISCUS will come on board – this is something we need to talk about.

[REDACTED]

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**From:** [REDACTED]  
**Sent:** Tuesday, March 18, 2014 7:18 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Moderate Alcohol Study

Hi [REDACTED],

I'm getting a little worried about the moderate alcohol study. I wonder if there is a way to introduce [REDACTED] to [REDACTED] and to the Beer people in order to have him convey his interest in the project. I think the goal would be for this to be a one-time thing for him. You and [REDACTED] have been the key advocates for the study, but I suspect they would like to hear from [REDACTED] before investing large sums of money.

Best,

[REDACTED]

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Favor  
**Date:** Monday, June 9, 2014 5:27:39 PM

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[REDACTED] THX so much! Best [REDACTED]

-----Original Message-----

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, June 09, 2014 03:15 PM Eastern Standard Time  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Favor

[REDACTED] and [REDACTED] – Here are my comments on items [REDACTED] highlighted in his text below. I look through the rest of the slides and I think they are fine:

- Slide 5 Bottom Right Box: “No one should be encouraged to drink for health benefits” I believe needs an edit to “Non-drinkers should not be encouraged to drink for health benefits”. I think this is more consistent with our current state of knowledge on light to moderate drinking, though if the box were bigger there would be many more qualifiers with this statement, e.g., who are not pregnant, who are of legal drinking age, who are not taking counter-indicated medications, who have a family history of alcohol use disorder, etc.
  - I would add also that if the Moderate Drinking Study we have been discussing to obtain industry financial support gets off the ground, we might be able to make this statement more definitive in the future.
- Slide 6 Middle Left Box: I am not sure you need this box at all, but if it is kept I have the following comments: “Advocacy Science” – I think this is an oxymoron – there is “advocacy” and there is “science”. What we don’t do is support “advocacy”. We do support “science” or more to the point “policy research” to achieve scientific findings that can inform the best policy measures. But policy is always a compromise between the scientific research findings and public needs (otherwise we would have a universal 15 mile per hour speed limit). Next: “Unfounded Research” – I would just drop this – it is an inherently obvious statement.
- Slide 17, right 2 boxes – I would drop these – DISCUS has a strong displeasure with both of these group and they are only 2 sources from which we obtain data, why highlight them!
- Slide 19: Marijuana – Excellent and Important Added Slide.

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, June 09, 2014 1:14 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Favor

[REDACTED]: Tomorrow evening is my 15minute Discus talk. Here is my second draft, with help from colleagues on the editing. Everything after thank you is likely not to be shown. The only real changes from my Friends of NIAAA talk are slide 5 bottom right box, slide 6 middle left box, slide 17 right two boxes and slide 19 addition of a marijuana slide. Are these tweaks ok? Is the talk ok? Thoughts. I would be very grateful for your input thanks best wishes [REDACTED]

## **SECTION (b):**

Key documents related to funding opportunity development and application process

- June 9, 2013 emails from NIAAA senior staff members copying other NIAAA staff members and select extramural PIs (including eventual lead of MACH trial) about potential activity codes to use for studies
- June 30, 2013 email among members of NIAAA senior staff
  - One NIAAA senior staff member describes how to expedite issuing a U34 planning grant funding opportunity announcement by signing on to an existing NIAMS U34 FOA, pending [DIAGEO contact] decision
  - This staff member writes,
    - “I think the PI can easily meet that, given that we have gone over in a lot of detail what the ultimate RCT should look like; plus that tight a timeframe would discourage other applicants who have not begun to think about this idea yet!”
    - Refers to ‘our applicant’
  - This staff member also asks about setting up a meeting with the group, and whether to include [an NIAAA office director] and writes “....if you think [office director] should be there too, that’s okay with me, but remember that he knows NOTHING about the possible funding source, and we should probably keep it that way for now.”

**[note: Notice of NIAAA sign-on to U34 was published July 12, 2013.]**

- July 23, 2013 email exchange between two NIAAA senior staff members regarding planning a personal trip to Boston and meeting with a U34 applicant
- August 12, 2015 emails between NIAAA senior staff member and eventual PI about U10 due date
  - Staff member updates investigator about the development of the U10 funding opportunity and likely due date

**[notes: U10 FOA was posted October 5, 2015, with an earliest submission date of December 12, 2015. MACH U10 application was received December 18, 2015. ]**

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@bidmc.harvard.edu"; [REDACTED]@yale.edu"  
**Cc:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Re: Your thoughts?  
**Date:** Sunday, June 9, 2013 9:27:26 PM  
**Sensitivity:** Confidential

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I meant U34, not R34,

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Sunday, June 09, 2013 09:24 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@bidmc.harvard.edu  
[REDACTED]@bidmc.harvard.edu>; [REDACTED]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Your thoughts?

Ok, here are some preliminary thoughts:

- 1) The R-34 seems to be for Phase III clinical trials – can this be considered a Phase III trial? Here are the NIH definitions:
  - **Phase I:** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
  - **Phase II:** The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
  - **Phase III:** The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
  - **Phase IV:** Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.
- 2) Or can R34's be used for other phases? This we would need to explore. I like it as a planning tool for a number of reasons and it has a 1 year time frame, which would mean that the team would have to focus. It also allows substantial NIAAA staff involvement.
- 3) In past collaborative projects I have been involved in, we used the U 01 mechanism (College Drinking Prevention Initiative (I was staff collaborator on several of them)) and just the regular R mechanism (21, 25, and 03 – Collaborative Academic Emergency Medicine project) with informal involvement of NIAAA staff (me). Individual circumstances allowed these to work just fine, but I prefer the formal staff involvement for this project. The fact that we competed these did not get in the way of ultimately having the grants go to those we wanted them to go to, as we were proactive in recruiting those investigators we wanted to submit applications, and they scored better (which is why we wanted them involved in the first place). In a few cases we actually got applications with good ideas we did not think of, so the process made the final outcome stronger. We worded the FOA such that it gave the advantage to those investigators who really understood the objectives of the project and were able to put together applications that met the criteria. The reviews went well, likely due to the fact that [REDACTED], who was [REDACTED] at the time, really understood what we were trying to do and got excellent reviewers who also understood.

- 4) I like the U10. The UM1 may not be what we need - it is for complex clinical trials.
- 5) More to come.

From: [REDACTED] (NIH/NIAAA) [E]

Sent: Sunday, June 09, 2013 4:11 PM

To: [REDACTED]@bidmc.harvard.edu; [REDACTED] (NIH/NIAAA) [E]; [REDACTED]

Cc: [REDACTED] (NIH/NIAAA) [E]

Subject: Your thoughts?

Importance: High

Sensitivity: Confidential

I am thinking first the U34, to put the protocol design together, and then either the U10, U18, or UM1 (See attachment table). I am not at all familiar with the UM1 – I don't think NIAAA has done them, but I am still looking into that. **Do any of you see anything in the descriptions that make one or another either more or less appropriate?** I also need to find out more about how the U34 works – as in, do we first need to have the final consortium in place (i.e., competitively selected) and then pull people from that to work on the design? Or do we compete the U34, and thus possibly have the design decided by people who do not later make the actual consortium cut? Or can we just deliberately select specific people for the U34 – obviously they can't really submit a design application, if that's the point of the funding in the first place, plus the whole point of the U is to have substantial staff input (i.e., [REDACTED] & me) into the design? The only details I can find are for investigator-initiated R34s (<http://grants.nih.gov/grants/funding/r34.htm>); the activities expected/covered would be the same, but the switch to a U (i.e., staff involvement) and to not-necessarily investigator initiated (although that may still be an option --- and would solve the issue of having to compete it to others) may lead to some differences that need to be spelled out in the FOA (<http://grants.nih.gov/grants/guide/pa-files/PA-09-186.html>). [REDACTED], you have been involved in some multi-site consortia and/or U things, I think...do you have any unique insights here?

I have also included info in the table on the U19, but that is described elsewhere as a “multi-project grant” (details copied below), which entails some specifics that I suspect may not be a good fit (the first bullet point might be something than can be worked around, but the 3<sup>rd</sup> bullet could make things complicated, particularly when dealing internationally)

## Features of Multiproject Grants

Multiproject grants share the following features:

- At least two interrelated research projects (unless stated otherwise in the FOA) related to a theme with each capable of standing on its own scientific merit but complementing one another.
- Collaboration and interaction among projects and investigators to achieve a common goal.
- One grantee institution that will be legally and financially responsible for the use of funds.
- Support as needed for shared resources—core resources or facilities—that provide services or resources to at least two research projects.

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [C]  
**Subject:** Following up, since I haven't heard back from you ...  
**Date:** Tuesday, July 2, 2013 10:48:45 AM  
**Sensitivity:** Confidential

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Sunday, June 30, 2013 7:40 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** Update on my project -- is Tuesday meeting OK?  
**Importance:** High  
**Sensitivity:** Confidential

[REDACTED]'s people are VERY interested. To the extent that they asked her to NOT bring it up to the reps from other places, because they are thinking that they would like to do it all themselves, to "look good" amongst the competition. But we won't have a definite answer for another 10 days to 2 weeks...apparently she presented it to the U.S. team, but as you are aware, they are a global group; she is taking it to the London people now (was already scheduled to go there, so no, we are not *that* fabulous that she scheduled a special trip on our behalf ... LOL!), and then also will be at that Paris conference that [REDACTED] isn't going to...so we won't know more until after she gets back.

Meanwhile, we have found an existing U34 FOA that we can "sign on to", which according to [REDACTED], eliminates the OER/GPS bureaucratic time frame of getting our own out there, and so speeds up the process considerably. [REDACTED] and I think that we should release this FOA immediately, rather than wait for [REDACTED]'s response, for several reasons:

1. It will move the process along much more quickly, and will allow us to get to the Feb Council, rather than have to wait till June (yes, if the funding we are expecting comes I suppose we could skip any Council review since it will have at least had an official peer review, but we can make that decision later...this 'quick' schedule at least has us in place to go with the full-bureaucracy route if need be).
2. If [REDACTED] does fall through, we still have time to look into those other places for the final project, but to wait for firm funding before we even move initially on the planning stage could take many more months.
3. If we have no money in place by the time the U34 needs to be funded, it will be a relatively "small" grant, that NIAAA could fund on its own anyway (and [REDACTED] tells me that if we do, and then the other funds actually do come through in the same FY, they could be used to reimburse the RPG budget).
4. Finally, even if we wind up paying for the U34 ourselves, and then no other money materializes, the U34 makes it clear that it in no way guarantees that a follow-up U10 (the actual clinical trial) will also be funded (or even FOA'd). So, we can just quit there...or, if the overall budget scenario has changed by then (since it would be FY 15) we could look into all-NIH funding (us, NHLBI, NIDDK, NINDS), and we would already have a fully-designed protocol "ready", so those places would be less likely to be able to turn the project into something totally useless.

So, we need to make some decisions **now** about this U34:

Here is the link to the existing one that we would be signing on to <http://grants.nih.gov/grants/guide/pa-files/PAR-11-169.html> ([REDACTED] said this was the best one out of several choices, because it was the most generic, plus it was already a U34 -- the others were R34s, which we would then have to convert upon award, which

is not difficult but adds a step that we can avoid here). Apparently we (████) just would notify NIAMS – I don't think they can refuse, so that shouldn't be an issue. Then we release a "Notice" to the NIH Guide that says what the changes are for us. That is the document I have attached; **what we need a decision on is the dollar amount and the allowable term we want to go with.** We can either stay with the original FOA's language, which is: "*Budgets for direct costs of up to \$250,000 per year and a project duration of up to two years may be requested for a maximum of \$500,000 direct costs over a two-year project period.*" Or we can choose our own. I would be fine with a one-year term; I think the PI can easily meet that, given that we have gone over in a lot of detail what the ultimate RCT should look like; plus that tight a timeframe would discourage other applicants who have not even begun to think about this idea yet! As to the dollars, I would like to keep the statement at "direct costs of up to \$250,000", but I am expecting that the application would actually come in at less – he and I had originally been talking in terms of "\$100,000 +" for direct, and he wasn't balking – but that was also totally out of the blue, so I'd rather have the leeway in there to see what it actually prices out at once the writing starts filling in the blanks with real people and their time-commitment costs. As for the dates (receipt, review, Council), █████ says those are okay.

The second attached document is the stuff we would have put in if we were writing our own brand-new FOA, and it is what I expect our applicant to address. If we have several applicant groups requesting approval to submit, this information will be conveyed to all of them in the "conversation with staff" that we are requiring as part of that submission-approval process. (It is obviously way too much to put in as added text to the FOA – doesn't really change the nature of the PAR, but I suspect OER nonetheless would have a fit with that much verbiage accompanying a "sign-on" notice.).

**So, assuming you have time to look at the various attachments before then, can we meet sometime Tuesday for a decision?** (████, you, me... █████ if he needs to be there re: the dollar decision, or just in general); if you think █████ should be there too, that's okay with me, but remember that he knows NOTHING about the possible funding source, and we should probably keep it that way for now.

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: What are you doing August 16?  
**Date:** Tuesday, July 23, 2013 9:40:00 PM

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I could do it - I am off and did not have plans to go anywhere. I could fly or drive.

-----Original Message-----

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Tuesday, July 23, 2013 7:28 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** What are you doing August 16?

I am going to Boston for a brief "vacation". It would be entirely coincidental if I happened to spend a day with some friends who might be in the process of writing a U34 grant application, and if we also just happened to have some "hypothetical" discussions about details of such a study. This is a purely personal, i.e., NOT NIAAA-funded or authorized, trip. If you are interested in arranging your own such trip at the same time (which, if at all possible, would be very useful), let me know and I will give you the logistics details.

sent via BlackBerry



**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] @bidmc.harvard.edu  
**Subject:** Re: Foa  
**Date:** Wednesday, August 12, 2015 7:52:34 PM

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Ok. I forgot to ask [REDACTED] -we need his buy-in. I will speak with him in the am.  
Fyi- I leave for Sydney Aus on friday and will be back on the 24th.

Sent from my BlackBerry 10 smartphone.

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**From:** [REDACTED] @bidmc.harvard.edu  
**Sent:** Wednesday, August 12, 2015 7:02 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Foa

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No problem. I think we'll be OK.

Just remembered a question I think I posed but forgot to ask again – what do you think about a U13 for a meeting next year in conjunction with ISBRA in Berlin? It would be the right place and the right time (just before enrollment begins) and definitely of interest to that crowd if we were actually starting a trial. It would shrink our budget a bit, although I realize it basically just taps another NIAAA pot.

[REDACTED]

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**From:** [REDACTED] (NIH/NIAAA) [E] [mailto:[REDACTED]@willco.niaaa.nih.gov]  
**Sent:** Wednesday, August 12, 2015 2:40 PM  
**To:** [REDACTED]  
**Subject:** FW: Foa

Ignore what I said in my earlier email below. You should still operate under a mid-November receipt date for now.

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Wednesday, August 12, 2015 10:54 AM  
**Subject:** Foa

Have you guys submitted a complex app like this will be electronically before? We are being advised it can take 4 to 6 months to get one of these developed and submitted with all of the budgets, etc. They are suggesting a January receipt date.

Sent from my BlackBerry 10 smartphone.

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**SECTION (c):**

Emails on summary statement response discussion between NIAAA program staff and PI, and on Council review

- January 14, 2014 emails between NIAAA senior staff member and PI discussing writing responses to peer review critiques
- April 2016 emails discussing Council review of MACH U10 application

**From:** [REDACTED]@bidmc.harvard.edu  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@hsph.harvard.edu  
**Cc:** [REDACTED]@bidmc.harvard.edu  
**Subject:** RE: Response to reviewer comments on U34 app  
**Date:** Tuesday, January 14, 2014 3:32:45 AM  
**Attachments:** [U34 AA023258 response.docx](#)

---

[REDACTED], here's a draft for the U34. I tried to be discrete about the industry stuff.

[REDACTED], can you have a look and get it signed? I'll throw together a cover or you can use the one from the U34 itself :)

I'll look at the R13 next.

---

**From:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@willco.niaaa.nih.gov]  
**Sent:** Monday, January 13, 2014 5:03 PM  
**To:** [REDACTED]  
**Subject:** RE: Response to reviewer comments on U34 app

[REDACTED]:

Do not worry about responding to the comments from Reviewer #3 about the alcohol industry. They are inappropriate comments and they should not have been allowed into the discussion.

[REDACTED]

[REDACTED]  
National Institute on Alcohol Abuse and Alcoholism  
U.S. National Institutes of Health

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**From:** [REDACTED] (NIH/NIAAA) [C]  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: NIAAA Advisory Council Meeting Closed Session Teleconference\_April 20\_2016  
**Date:** Wednesday, April 20, 2016 3:03:00 PM

---

Indeed!

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Wednesday, April 20, 2016 2:58 PM  
**To:** [REDACTED] (NIH/NIAAA) [C] [REDACTED]@willco.niaaa.nih.gov>; [REDACTED] (NIH/NIAAA) [E] [REDACTED]@willco.niaaa.nih.gov>; [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov>  
**Cc:** [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov>; [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov>  
**Subject:** RE: NIAAA Advisory Council Meeting Closed Session Teleconference\_April 20\_2016

He is one of our new council members. He must have forgotten what council members are expected to do. I had explained it already.

---

**From:** [REDACTED] (NIH/NIAAA) [C]  
**Sent:** Wednesday, April 20, 2016 2:42 PM  
**To:** [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov>; [REDACTED] (NIH/NIAAA) [E] [REDACTED]@willco.niaaa.nih.gov>; [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov>  
**Cc:** [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov>; [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov>  
**Subject:** RE: NIAAA Advisory Council Meeting Closed Session Teleconference\_April 20\_2016

[REDACTED]

Had he been on the call his concerns would have been answered. Also, he was looking at the project as if he was on the Initial Review Committee rather than Council. In any event, he was not on so the vote does not count, as you noted.

[REDACTED]

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Wednesday, April 20, 2016 2:17 PM  
**To:** [REDACTED] (NIH/NIAAA) [E] [REDACTED]@willco.niaaa.nih.gov>; [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov>; [REDACTED] (NIH/NIAAA) [C] [REDACTED]@willco.niaaa.nih.gov>  
**Cc:** [REDACTED] (NIH/NIAAA) [E] <[REDACTED]@mail.nih.gov>; [REDACTED] (NIH/NIAAA) [E] <[REDACTED]@mail.nih.gov>  
**Subject:** FW: NIAAA Advisory Council Meeting Closed Session Teleconference\_April 20\_2016  
**Importance:** High

█ was too late to call in and sent his comment. His vote does not count since he was not in the meeting.

█

---

**From:** █ [mailto:█@edu]  
**Sent:** Wednesday, April 20, 2016 2:14 PM  
**To:** █ (NIH/NIAAA) [E] █@mail.nih.gov>  
**Cc:** █ (NIH/NIAAA) [E] █@nih.gov>  
**Subject:** Re: NIAAA Advisory Council Meeting Closed Session Teleconference\_April 20\_2016  
**Importance:** High

Hi █,

Sorry I missed the call. I was confused about EST and CST. It is probably too late, but from what I read I would not approve this proposal. It is clear that the group does not have a good way to measure the dose of ETOH. You might expect this to generate more variance in the data. It could also lead to increased dosing which would perhaps change the skewness of the distribution. So the analysis becomes a statistical problem where population parameters can only be estimated (which is true of any data set) in the presence of lots of noise.

Forms are on their way.

█

█

On Apr 19, 2016, at 8:58 AM, █ (NIH/NIAAA) [E] <█@mail.nih.gov> wrote:

Just a reminder about the Closed Session meeting of the NCAA for 2016\_04 council tomorrow, April 20, 2016. Please call **1 866 827 9943** at 12:50 PM. We will start promptly at 1:00 PM Eastern Time.

For those who have not sent in the COI and honorarium forms, please do so as soon as possible. We look forward to an interesting discussion tomorrow.

The agenda is as follows.

**NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND  
ALCOHOLISM**

**CLOSED SESSION COUNCIL 2016/04  
REVIEW OF GRANT APPLICATIONS**

**1866 827 9943; █**

**Wednesday, April 20, 2016  
1:00-2:00**

1:00 PM [REDACTED] Call to Order and Introduction to Closed Meeting – Dr.

1:10 [REDACTED] Review of Confidentiality and Conflict of Interest – Dr.

1:15 [REDACTED] Review of Grant Applications- Dr.

Office of the Director- Dr.

[REDACTED]  
[1-U10-AA025286-01](#) [REDACTED]  
The Moderate Alcohol and Cardiovascular Health Trial  
(PCC AL M)

2:00 PM Adjourn

Best regards,

[REDACTED]

<NCAA Honorarium Form\_2016\_04 Council\_FINAL.docx><Post COI.pdf>

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** FW: NIAAA Advisory Council Meeting Closed Session Teleconference\_April 20\_2016  
**Date:** Wednesday, April 20, 2016 2:22:20 PM  
**Importance:** High

---

[REDACTED]: Again thanks for a masterful job. Could you please respond to [REDACTED] and [REDACTED] with a copy of your text to the council and a direct rebuttal of their points (I would keep that part short). Thanks best wishes [REDACTED]

Ps feel free to cc me in the response to them

---

**From:** [REDACTED]@edu>  
**Date:** Wednesday, April 20, 2016 at 2:14 PM  
**To:** [REDACTED]@nih.gov>  
**Cc:** "[REDACTED] (NIH/NIAAA) [E]" [REDACTED]@nih.gov>  
**Subject:** Re: NIAAA Advisory Council Meeting Closed Session Teleconference\_April 20\_2016

Hi [REDACTED]

Sorry I missed the call. I was confused about EST and CST. It is probably too late, but from what I read I would not approve this proposal. It is clear that the group does not have a good way to measure the dose of ETOH. You might expect this to generate more variance in the data. It could also lead to increased dosing which would perhaps change the skewness of the distribution. So the analysis becomes a statistical problem where population parameters can only be estimated (which is true of any data set) in the presence of lots of noise.

Forms are on their way.

[REDACTED]

[REDACTED]

On Apr 19, 2016, at 8:58 AM, [REDACTED] (NIH/NIAAA) [E] [REDACTED]@mail.nih.gov> wrote:

Just a reminder about the Closed Session meeting of the NCAA for 2016\_04 council tomorrow, April 20, 2016. Please call **1 866 827 9943** at 12:50 PM. We will start promptly at 1:00 PM Eastern Time.

For those who have not sent in the COI and honorarium forms, please do so as soon as possible. We look forward to an interesting discussion tomorrow.

The agenda is as follows.

**NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND  
ALCOHOLISM  
CLOSED SESSION COUNCIL 2016/04  
REVIEW OF GRANT APPLICATIONS  
1866 827 9943; 5635 Fishers Lane # 3002  
Wednesday, April 20, 2016  
1:00-2:00**

1:00 PM [REDACTED] Call to Order and Introduction to Closed Meeting – Dr.

1:10 [REDACTED] Review of Confidentiality and Conflict of Interest – Dr.

1:15 [REDACTED] Review of Grant Applications- Dr.

[REDACTED] Office of the Director- Dr.

[1-U10-AA025286-01](#) [REDACTED]  
The Moderate Alcohol and Cardiovascular Health Trial  
(PCC AL M)

2:00 PM Adjourn

Best regards,

[REDACTED]

<NCAA Honorarium Form\_2016\_04 Council\_FINAL.docx><Post COI.pdf>



**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] edu; [REDACTED] org  
**Cc:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** response to comments on application 1U01AA025286  
**Date:** Friday, April 22, 2016 2:16:33 PM  
**Attachments:** [REDACTED] Councilpresentation.docx

---

Dear Drs. [REDACTED] and [REDACTED]:

Thank you for weighing in on the review of application 1U01AA025286-01. Since you were not able to be on the teleconference where the Advisory Council discussed this application, I will address the concerns that you emailed in to Dr. [REDACTED]. Also, attached for your information is a written transcript of the history and background of this application which, as you will see in the transcript, has some unique features.

As described in the transcript, there is a history as to why NIAAA is getting involved in answering the questions raised by conflicting observational studies that have reported protective effects for light to moderate alcohol consumption in the areas of CVD, Type 2 diabetes and overall mortality. Funds for the grant application under discussion will primarily come from private sources via donations to the Foundation for the NIH (80% of funding. NIAAA will contribute 20% of funds).

Now to address some of the concerns each of you raised (many of which were addressed during the discussion with other Council members on Wednesday's conference call):

1. Interactions effects with other drugs – Subjects will have a complete medical history at baseline and yearly medical exams. Data on smoking and use of medications and other drugs will be collected. A large portion of the sample will be recruited via primary care practice networks, so there will be a focus on health status.
2. Compliance/adherence is an important issue. It will be addressed at the outset by targeting individuals who are not alcohol naive, and yet drink in a light to moderate pattern. Subjects will be monitored closely via in person visits at 3 and 6 months, including laboratory tests (HDL-C) and will meet with health coaches to reiterate the importance of maintaining adherence to their assigned arm. Between visits subjects will receive electronic communications (participant choice of email, text or phone calls), where they will report consumption. EMA (ecological momentary assessment) has been shown in studies to reduce heavy drinking, suggesting that it will serve both monitoring and adherence functions. Intervention arm can consume from 5-13 drinks per week and still be in compliance. Controls will be in compliance at <1 drink per week. Since subjects can choose beverage type there is a stronger likelihood of compliance. There is a sophisticated plan described in the application to deal with subjects in each arm who's reported drinking is not adhering to the protocol, in order to bring them back in line. The study team has a great deal of experience with keeping subjects on track in large, long term RCT's on lifestyle interventions, such as Women's Health Initiative and the PREDIMED study of Mediterranean diet.
3. The study outcomes are focused on whether or not there is a benefit as reported in many observational studies. The study is not powered to identify negative health effects. For example, breast cancer is currently the only cancer associated with light to moderate drinking, and the study would need to be twice the order of magnitude to demonstrate whether or not this is true. It would likely be impossible to get consent from subjects to be in such a study once study aims are revealed to them. In the current design, individuals with any risk for breast cancer are excluded.
4. Most reviewers considered the multi-cultural aspect of the study a strength. Site differences are addressed through block randomization, as well as the large sample size.
5. The sick quitter argument was settled fifteen years ago as this was one of the first issues raised when the observational data seemed to show a protective effect of alcohol. Studies since then have controlled for this effect.

6. Data on each subject's history of alcohol use will be collected.
7. Alcohol consumption will be reported frequently, and all types of beverages and amounts will be included. Abstainers will be counseled to abstain from all alcohol. The vanguard year of the study will determine feasibility of adherence and an external DSMB will monitor and report to NIH and the study will be stopped if it cannot be done.
8. The definition of moderate use in this study is clearly spelled out in the application as 14 grams of alcohol per day.
9. As previously stated, cumulative exposures will be accounted for in alcohol consumption histories.

The manner in which dose is measured will be from subject education on what is considered a dose for the study as well as frequent collection of consumption by self-report. Biomarker (HDL-C) will be used to corroborate self-report data. This is actually a more rigorous method than any previous epidemiological studies that report either positive or negative effects, upon which our current understanding is based.

Thanks for your comments, I am happy to address any other questions you may have.



National Institute on Alcohol Abuse and Alcoholism

As many of you are aware, the question of whether or not there are protective benefits from low to moderate consumption of alcohol for cardiovascular disease and diabetes, as well as other health conditions remains controversial.

Several epidemiological studies since the 1970's have consistently shown lower CVD risk and lower overall mortality in those who drink moderately when compared to abstainers and heavy drinkers. This effect remains even after controlling for lifestyle and other risk factors, including data from individuals who abstain as a result of serious illness. Recently, this same protective benefit has been seen for Type 2 Diabetes and there was a short term clinical trial published late last year that seems to confirm this observation. In addition, there is a large and growing body of basic science and human laboratory studies that have identified plausible mechanisms for the observed protective effects. Currently, a number of physicians around the world recommend light drinking to their patients at risk for heart attack and ischemic stroke (i.e. Walter Koroshetz testified before Congress that he advises his patients at risk for ischemic stroke to drink a glass of wine every evening with dinner.)

Nevertheless, controversy remains as there are additional observational studies published from time to time that seem to contradict the protective benefits observed. Most recently, Holmes et al which used Mendelian randomization analysis on a review of previous studies and found that the risk of CVD and mortality increased with any drinking.

There have been a number of calls for an RCT to answer the questions raised in the contradictory findings described. Most recently in ACER (1/15) and by members of the U.S. Congress in significant item in the 2015 appropriations language (which you received before today's meeting).

To do a clinical trial well, and of a magnitude to provide enough power to answer the questions, is very expensive. NIAAA funded a conference grant as well as a U34 planning grant in 2014 to consider the feasibility and logistical issues. Both brought together a number of outstanding investigators from major clinical trials (i.e. SPRINT; PREDIMED) who were very interested in the scientific issues of designing and conducting such a study. NIAAA also contacted other NIH institutes to see if they would join in and interest was expressed by NINDS and NIA who added scientific staff to the U34 planning grant.

The Foundation for the NIH was contacted by NIAAA after staff learned that some companies in the alcohol beverage industry were interested in funding an RCT. They are interested in settling the controversy, despite the risk that the answer may not benefit their product. FNIH has a rigorous two-layer review process before it will consider accepting funds to be used in an NIH study. Dr. Collins has a group composed of himself and three additional IC directors that look at a formal Request for Collaboration, and then the FNIH board of Directors has their own review process. There is a strict policy that funders have total hands off of any potential study design and can have no knowledge or influence of the review and award and grants management process throughout the life of the study. Indeed the funders are aware that if they are involved in any way, the results will not be taken seriously. Precedents for industry funding via the FNIH include a Mars Corporation funded study of chocolate, a Quaker Oats funded clinical trial on breakfast and weight loss, and NFL funded studies on CTE.

NIAAA completed the FNIH review process in summer of 2015 and FNIH proceeded to contact potential donors. They received commitment letters from six global alcohol producers for ten years of funding (\$8 million per year for 10 years) for a long term RCT. It is important to note that FNIH will continue to solicit funds from private companies, including the health insurance industry and others interested in this question. As part of the agreement with FNIH, NIAAA agreed to commit some of its own funds (\$2million per year for 10 years, an amount that is standard for RFA's – clinical trials can run \$6 million per year).

In the fall of 2015, NIAAA issued a program announcement indicating interest in reviewing applications for a U10 clinical trial research center. Recipients of the U34 planning grant applied in December 2015. The review took place at the end of March 2016. The FNIH informed NIAAA in January of the fact that the funds were in their bank account, and we would need to make an award in the first half of 2016 according to the agreement they signed with the donors. The application under discussion is for the first 5 years of funding for the study cores and for the initial nine sites. If all goes well with recruitment and compliance during the vanguard phase (first 9 months), NIAAA will issue a follow up PAR to fund 7 additional sites in order to reach the subject total.

The specific aims of the study are as follows:

- Global, six-year, balanced-design randomized trial, comparing the effects of one standard serving (~14 grams) of alcohol intake daily to abstinence on risk of CVD, diabetes, mortality, and related outcomes among 7,800 adults at above-average cardiovascular risk.
- To maximize feasibility and reflect actual use most closely, the test will be alcohol consumption per se compared to abstinence and thus, will offer participants flexibility in their choice of beverage, while employing novel and intensive yet efficient methods to monitor safety.
- **The Primary Specific Aim of this trial is to determine the effects of 14 gm of alcohol intake daily compared with abstinence on risk of major cardiovascular events or death (myocardial infarction, ischemic stroke, hospitalized angina, need for revascularization, or death) over an average of 6 years of follow-up among 7,800 adults aged  $\geq 50$  years with estimated 10-year CVD risk  $\geq 15\%$  or prevalent CVD  $> 6$  months prior to enrollment.**
- Secondary Aims will test the effects of alcohol on risks of incident diabetes and major cardiovascular events.
- Tertiary Aims will test risks of hard cardiovascular events and progression to impaired fasting glucose.
- Similar to other large randomized trials, we will establish ~16 centers worldwide using a stepped approach, with a 9-month vanguard phase among 7 centers in the US, Europe, Africa, and South America (in this application), followed by a second wave of additional sites to complete enrollment.
- Participants will be monitored for safety in multiple complementary ways, including brief electronic real-time reporting and validated yearly instruments and laboratory measures. There will be a DSMB to monitor the study and advise NIH.
- Team consisting of highly successful groups in the US and Europe to establish clinical, data, and biospecimen coordinating centers.
- Field centers include many of the most experienced clinical trialists anywhere, having worked on very large multi-site global trials including SPRINT – systolic blood pressure, and PREDIMED – Mediterranean diet, studies.

## SECTION (d):

Industry representative and NIAAA staff communication related to scientific planning/results of the study

- November 4, 2013 email exchange from Spirits EU leadership to NIAAA senior staff member
  - Spirits EU leadership writes NIAAA senior staff member expressing interest in proposed work NIAAA plans on a conference on the benefits of alcohol and “clinical trials to show the J curve in all its glory”
  - Email forwarded to another NIAAA senior staff member noting Spirits EU ‘interest in your study’
  
- July 17, 2014 email from NIAAA senior staff member to NIAAA senior staff members addressed “Dear team health benefits of drinking”
  - States inclination not to raise a BMJ essay with “Building 1” unless specifically asked
    - Essay referenced by Glymour (BMJ 2014; 349 doi: <https://doi.org/10.1136/bmj.g4334> (Published 10 July 2014)) is a comment on a paper by Holmes et al (BMJ 2014; 349 doi: <https://doi.org/10.1136/bmj.g4164> (Published 10 July 2014) ) concluding that “Individuals with a genetic variant associated with non-drinking and lower alcohol consumption had a more favourable cardiovascular profile and a reduced risk of coronary heart disease than those without the genetic variant. This suggests that reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health.”
  
- August 4, 2014 emails between eventual PI of MACH trial and International Center for Alcohol Policy (ICAP) – PI provides responses to address methodological issues raised by Diageo, DISCUS, ABI, and ICAP)
  
- December 8, 2014 conference call to discuss study
  - NIAAA senior staff members email to confirm joining the call
  - NIAAA senior staff member and eventual PI of MACH trial email discussing questions to be answered on the call
  
- February 26, 2015 – Emails between NIAAA senior staff member and eventual PI of MACH trial
  - NIAAA senior staff member asks investigator for edits to an email to send to “[first name]” (likely ICAP)
    - Includes a bullet that states ‘one of the important findings will be showing that moderate drinking is safe’, etc.

[REDACTED]

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, November 04, 2013 12:22 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: thank you

Could be either. When I mentioned funding to him in Paris, he asked me if we had approached DISCUS and/or OCAP. I will get back to him after you see what [REDACTED] is interested in – if he knows other distillers are going to be involved, it may help. I think we could get him on Ireland and Scotland and perhaps Russia, saying that if we had the funds, we could do an arm of the study that included Scotch, Whiskey, or Vodka.

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, November 04, 2013 12:16 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: thank you

Only if some purveyors of such give us adequate money to add sites in places where they are heavily used as the drink-of-choice. Can you tell if your contact in Europe was “interested” in the sense of hitting his ‘clients’ up for money, or just “interested” because the results would be helpful/needed, as long as someone else paid for them?

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, November 04, 2013 12:12 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: thank you

So – are you leaning towards including distilled spirits?

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, November 04, 2013 11:11 AM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: thank you

Excellent ! I would be happy to talk with him (or any of his folks..including by videoconference, which is what [REDACTED], [REDACTED], and I are doing for the European Beer people next week) if he wants our full dog-and-pony show.

She is on my calendar for 4 pm tomorrow....right after the Heineken meeting

---

**From:** [REDACTED] (NIH/NIAAA) [E]  
**Sent:** Monday, November 04, 2013 11:03 AM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** FW: thank you

This is the guy from Spirits EU – he is expressing interest in your study, and also he is letting [REDACTED] know they are interested.

Has she called you?

---

**From:** [REDACTED] [REDACTED]@spirits.eu]  
**Sent:** Monday, November 04, 2013 10:23 AM  
**To:** [REDACTED] [REDACTED] (NIH/NIAAA) [E]

**Cc:** [REDACTED]; [REDACTED]  
**Subject:** RE: thank you

Dear [REDACTED]

Always a pleasure.

Dear [REDACTED]

It was a great pleasure to meet you two weeks ago in Paris. I would like to say it was also a great pleasure to attend the OECD meeting itself, but my diplomacy only stretches so far...

For your information, I attach a copy of my follow-up note to [REDACTED] underlining the difficulties with their apparent acceptance of the consumption = harm equation. We will wait to see their revised draft on 12 November, but I am not holding my breath for any significant changes.

I wanted to follow up with you on two things, please:

- You mentioned the proposed work NIAAA plans on a conference on the benefits of alcohol (within the next year), and the possibility of clinical trials to show the J curve in all its glory. I just wanted to repeat our great interest in both of those initiatives, and I ask you to please keep me briefed on dates and plans as you proceed. I would be very happy to keep the sector in Europe advised on your work and proposals.
- Secondly, a question concerning the fiscal paper that OECD presented at the Experts meeting. [REDACTED] gave the impression that the OECD Health Committee had already largely approved that paper, and – subject to a few minor changes – it was already going to publication. Is that also your understanding? If so, did the Committee approve it in July, or back in December last year? As you imagine, we have grave concerns about the general nature of that paper and I was a little bit shocked to learn that it was a fait accompli. Why then, add something already decided to the meeting 2 weeks ago?

Concerning [REDACTED] suggestion for the drink and the meal, I think it's a great idea – and I suggest to rope in [REDACTED] also. That dinner is getting larger and larger. By the time we meet, who knows...?

Kind regards,

[REDACTED]

---

**From:** [REDACTED] [[mailto:\[REDACTED\]@diageo.com](mailto:[REDACTED]@diageo.com)]

**Sent:** 04 November 2013 15:49

**To:** [REDACTED]

**Cc:** [REDACTED] (NIH/NIAAA) [E]

**Subject:** thank you

Dear [REDACTED],

Again, thank you for a lovely lunch today and a fantastic discussion. I am cc'ing [REDACTED] so that you have her e-mail address. Maybe the next time we are all three in the same city we can go out and enjoy a drink and a meal and discuss everything but work!

With all the best, [REDACTED]



[REDACTED] PhD | [REDACTED] | **DIAGEO** | 600 Pennsylvania Avenue, SE, [REDACTED]  
Washington, DC 20003 [REDACTED] 3 | mobile [REDACTED] |

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** FW: beneficial effects of alcohol  
**Date:** Thursday, July 17, 2014 8:10:16 AM  
**Attachments:** [Alcohol and cardiovascular disease. The BMJ. Glymour. 2014.pdf](#)  
[Holmes2014 Association between alcohol and cardiovascular disease.pdf](#)

---

Dear team health benefits of drinking: This, below, derives from a picnic conversation with [REDACTED]. I apologize if I am failing at alerting everyone interested in this issue with my emails. My inclination is NOT to raise this paper (Glymour) with building 1 unless they specifically ask us but to be ready if they do. I think [REDACTED]'s cogent comments from yesterday evening say it all, so let us save them in case we are queried. Best wishes [REDACTED]

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**From:** <[REDACTED] [E] (NIH/NIAAA)" [REDACTED]@mail.nih.gov>  
**Date:** Thursday, July 17, 2014 at 12:46 AM  
**To:** "[REDACTED] (NIH/NIAAA) [E]" <[REDACTED]@nih.gov>  
**Subject:** beneficial effects of alcohol

Dear [REDACTED]

Following up on our conversation here are a few thoughts on the topic:

A large number of observational studies reported positive correlation between moderate level of alcohol consumption and beneficial cardiovascular indices, but the molecular underpinnings of these effects remain largely enigmatic. Besides, conclusions of these studies are stymied with numerous confounders (lifestyle, diet, genetic background, socioeconomic status etc.) that make them unfeasible to objectively establish causality between moderate alcohol drinking and beneficial cardiovascular outcomes based purely on epidemiological observations. Recent studies using mendelian randomization of ADH alleles, as a natural experiment reminiscent of randomized clinical trials also challenge this dogma, as they report negative association between moderate alcohol consumption and cardiovascular disease. Large scale randomized clinical trials could provide the best hope to effectively settle this important issue, but their feasibility remains uncertain. Even if causality is unequivocally proven between moderate drinking and cardiovascular benefits, recommendations for alcohol consumption need to take into consideration other, potentially elevated health risks associated with moderate alcohol drinking (e.g. increased occurrence of certain cancers and neurodegenerative diseases amongst others).

[REDACTED]

## EDITORIALS

### Alcohol and cardiovascular disease

New research tools will help us untangle this enigmatic association, eventually

M Maria Glymour *associate professor*

Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA 94115, USA

Many observational studies report that people who drink moderate amounts of alcohol have lower cardiovascular risk than non-drinkers,<sup>1</sup> but they cannot conclusively answer the most important question: will moderate drinking reduce cardiovascular risk? The distinction between the answers we derive from conventional observational studies (which are predictive) and the answers we need for improving health (which are causal) is fundamental. Mistaking predictive associations for cause and effect could, for example, lead us to confiscate matchbooks as a strategy to prevent lung cancer, because carrying matchbooks predicts future risk of lung cancer.

Recent decades have seen major breakthroughs in methods to evaluate cause and effect from observational studies.<sup>2</sup> Despite their potential scientific value, the proposed advances are controversial.<sup>3,4</sup> The paper by Holmes and colleagues (doi:10.1136/bmj.g4164) perfectly illustrates why.<sup>5</sup> Holmes and colleagues try to evaluate whether moderate drinking helps prevent cardiovascular disease using a mendelian randomisation design.<sup>6</sup> The paper explores only the direction of effects—whether drinking increases or decreases cardiovascular risk—because they omit the usual analysis in mendelian randomisation studies (instrumental variables analyses) which would estimate the magnitude of alcohol's effects.<sup>7,8</sup>

Mendelian randomisation studies treat genetic background as “quasi-experiments”, assuming that inheriting the A-allele of the *ADH1B* locus is equivalent to being randomly assigned to drink less alcohol. Holmes and colleagues find that A-allele carriers drink less and have lower cardiovascular risk. They conclude that drinking increases cardiovascular risk and prior observational evidence should be revisited. They draw this conclusion without ever presenting conventional analyses using reported drinking to predict coronary heart disease.

Holmes and colleagues' inferences rest on two assumptions, similar to those of a randomised controlled trial assigning individuals to treatment to reduce drinking, except here the *ADH1B* allele is the treatment. First, they assume the “trial” was randomised: that is, they assume that adults “assigned” the A-allele and controls not “assigned” the allele would have had identical cardiovascular risk without these assignments. Second, they assume that assignment to the allele had no effect on cardiovascular disease besides effects mediated by drinking.

Although the assumptions made in mendelian randomisation parallel the assumptions made about real treatments in randomised trials, those same assumptions are usually less plausible in mendelian randomisation studies and merit more scrutiny.

How do these compare to assumptions in conventional observational studies of drinking and cardiovascular disease? After all, new methods with somewhat implausible assumptions may be preferable to traditional methods resting on even less plausible assumptions. Although rarely stated explicitly, traditional observational studies—studies using drinking to predict cardiovascular disease—can explore cause and effect only by assuming that drinking is effectively randomly allocated. This boils down to assuming that we have appropriately accounted for every factor that influences both drinking and cardiovascular disease (confounders), an almost impossible task in observational research despite sophisticated statistical techniques such as propensity scores used to account for multiple covariates.

Both conventional and mendelian randomisation approaches thus rely heavily on unprovable assumptions, so controversy is unsurprising. Because the two sets of assumptions are very different, results are most convincing when both approaches give the same answer. Holmes and colleagues' findings suggest the answers diverge for this research question, however, so we must choose which is most plausible.

Challenging assumptions is an important part of interpreting all observational work, and justifying assumptions is an important part of reporting it. For example, mendelian randomisation studies assume that effects of *ADH1B* polymorphisms on cardiovascular disease risk operate only via drinking. Holmes and colleagues try to show this by exploring whether *ADH1B* predicts coronary heart disease among people with similar levels of alcohol consumption. Although estimates are imprecise, results (figs 1 and 2 of paper) suggest *ADH1B* predicts cardiovascular disease risk even within groups of people with similar alcohol use. This should make us cautious about the conclusions—the allele should not predict cardiovascular risk among adults who all drink roughly the same amount. But we cannot be sure because alcohol use is imperfectly measured, and it's still possible that, for example, moderate drinkers with

the A-allele drink slightly less than moderate drinkers without it.

There is a further problem with this particular allele as a proxy for alcohol consumption. *ADH1B* polymorphisms influence alcohol metabolism, and therefore influence exposure to both alcohol and its metabolites.<sup>9</sup> If these metabolites influence risk of cardiovascular disease, one of the core assumptions underlying mendelian randomisation is violated.

One of the most surprising conclusions by Holmes et al is that reduced drinking is beneficial even for light to moderate drinkers. The analyses presented in the paper cannot establish this claim, however, because they rely on how much alcohol use individuals actually report. To evaluate whether effects of reducing drinking for moderate drinkers are similar to effects for heavy drinkers, one approach would define moderate and heavy drinking as separate variables and conduct a multiple-variable instrumental variables analysis.<sup>10</sup>

Holmes and colleagues present provocative and innovative analyses. Their approach has many limitations, but so do conventional observational designs. The findings challenge evidence from epidemiological studies and show the need for new, more critical assessments of whether the enigmatic associations between alcohol intake and cardiovascular disease are causal. Firm conclusions are still difficult, and the next step is to integrate findings from mendelian randomisation and conventional study designs. Large scale randomised controlled trials of alcohol use are unlikely, if not impossible, so we must make the most informed inferences we can, using observational and quasi-experimental evidence on this important research question. Combining evidence from multiple research designs (that is, "design diversity") will prove enlightening in the long run, even if conclusions are puzzlingly inconsistent and difficult to interpret in the short run. Truly novel studies, such as the study by Holmes and colleagues, are therefore critical contributions to the research base.

Provenance and peer review: Commissioned, not externally peer reviewed.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests have no relevant interests to declare.

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- 9 Kang G, Bae KY, Kim SW, Kim J, Shin HY, Kim JM, et al. Effect of the allelic variant of alcohol dehydrogenase ADH1B\*2 on ethanol metabolism. *Alcohol Clin Exp Res* 2014;38:1502-9.
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Cite this as: *BMJ* 2014;349:g4334

## Related links

### bmj.com/archive

- Research: Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study (BMJ 2011;342:d1584)
- Research: Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis (BMJ 2011;342:d671)
- Research: Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies (BMJ 2011;342:d636)
- Research: Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME) (BMJ 2010;341:c6077)

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**From:** [REDACTED]  
**To:** [REDACTED] @bidmc.harvard.edu  
**Cc:** [REDACTED] @hsph.harvard.edu; [REDACTED] (NIH/NIAAA) [REDACTED] [REDACTED] (NIH/NIAAA) [REDACTED]  
**Subject:** RE: Moderate drinking RCT and methodological issues  
**Date:** Monday, August 4, 2014 12:28:32 PM

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Dear [REDACTED],

Many thanks for your message and for the very comprehensive and clear responses to the questions I shared with you. We will be passing these along to the various sponsors and I hope that your explanations will satisfy any queries they might have.

Should there be a desire to convene a call or to address any additional issues, we will do our best to arrange it.

In any event, we will be in touch with any updates and further information.

Kind regards,

[REDACTED]

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**From:** [REDACTED] @bidmc.harvard.edu [REDACTED] @bidmc.harvard.edu]  
**Sent:** Friday, August 01, 2014 2:38 PM  
**To:** [REDACTED]  
**Cc:** [REDACTED] @hsph.harvard.edu; [REDACTED] @willco.niaaa.nih.gov; [REDACTED] @yale.edu; [REDACTED] @willco.niaaa.nih.gov  
**Subject:** RE: Moderate drinking RCT and methodological issues

[REDACTED],

Please find attached responses to the important issues that your group raised. I hope they are of appropriate length and depth, but if not, do let us know. Our research group discussed them on our weekly calls, and I believe they represent the consensus of our investigative team, but we want to be sure to address your questions as carefully and as completely as possible.

We're very grateful for your dedication and concern on our behalf. We look forward to speaking further about these issues or others that may arise in your discussions.

With all best wishes,

[REDACTED]

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**From:** [REDACTED] [REDACTED] @icap.org]  
**Sent:** Tuesday, July 15, 2014 5:06 PM  
**To:** [REDACTED]  
**Cc:** [REDACTED] @hsph.harvard.edu; [REDACTED] @willco.niaaa.nih.gov; [REDACTED] @yale.edu  
**Subject:** RE: Moderate drinking RCT and methodological issues

Dear [REDACTED],

Many thanks for your message and for sharing the information on the RCT. I hope that by now your jet lag is but a distant memory.

I appreciate the agenda from the meeting and list of speakers, which are both very useful and reassuring. I will share them.

The questions that have been raised relate to the design of the trial. One limitation we have on this end is that we have only seen the slides that were prepared in various iterations for industry briefings and, as a result, lack the depth and detail that you would have included had you not been addressing a lay audience. I have no doubt that you have thought all of these through, so am sure that the questions can be dealt with easily.

I am attaching a list of the issues that were raised during the recent call and hope that they will give you an idea of some of the concerns. Again, I imagine they have already been tackled. In the spirit of evenhandedness, the questions reflect input from all four members of the group ([REDACTED] Diageo; [REDACTED] DISCUS; [REDACTED] ABI; and me).

Once you have read through this list, we can convene a conference call to discuss. However, if you prefer, you can respond in writing. Given that it's summer and people are likely to be out, the latter option might be preferable at this stage. We can always convene a call in due course.

I look forward to hearing from you.

Kind regards,

[REDACTED]

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**From:** [REDACTED]@bidmc.harvard.edu [REDACTED]@bidmc.harvard.edu]  
**Sent:** Friday, July 11, 2014 2:56 PM  
**To:** [REDACTED] [REDACTED]@yale.edu  
**Cc:** [REDACTED]hsph.harvard.edu; [REDACTED]@willco.niaaa.nih.gov  
**Subject:** RE: Moderate drinking RCT and methodological issues

[REDACTED]

I'm finally back at work today. Let me reiterate that I'm very grateful to you, [REDACTED] and many others for helping to maintain enthusiasm for this project.

I have attached the agenda from the Seattle meeting, although we went out of order to accommodate various schedules so this does not perfectly reflect the day's discussions. A number of other individuals attended, including a few members of Suntory and several NIAAA staff (along with [REDACTED]), but I have only included our invited group here, as I only have the names of those with

whom I communicated in advance.

As you can see, we had a stellar group of speakers who came from Europe, South America, Japan, and across the U.S. specifically for this symposium. I think it fair to say that there was great enthusiasm in the room for the project, with a rich discussion. NIAAA in particular demonstrated again its commitment; [REDACTED] attended much of the meeting, and several NIAAA staff members were present all day.

I have copies of the actual talks and can also prepare PDF's of those, although much of the discussion isn't captured by those – do let me know if you'd like to see any of them based on the titles in the agenda.

With that said, we have not yet prepared a formal summary of the meeting, as I left just 3 days later and we have yet to receive the transcription of the recorded proceedings. As such, I can't easily provide a quick summary of our day's discussions, although they addressed essentially every topic listed on the agenda. For example, we discussed measures of compliance at length, including the utility of ethyl glucuronides, HDL-C, tartaric acid, and others, and hence we have a number of strong options, although it is likely that we will use several of these in different ways with more to come. We also did not prepare a protocol in the traditional scientific sense of a manual of operations or a scientific research plan, although the symposium was not explicitly intended for that.

I will forward our detailed summary as soon as I can, although I'm not sure it will exactly meet your needs. Our goal over this planning grant year (and for this symposium, as a kick-start to that) is to finalize an operational protocol, but the specifics of that goal and its timing differ from your needs in demonstrating strong scientific underpinnings and rationale for this project. Given that, it might indeed be best for [REDACTED] and I (and probably [REDACTED] and [REDACTED]) to hear more about the topics you'd like us to cover and the degree of clarification needed. We can then provide more targeted and detailed descriptions of what we covered in Seattle and what we've already discussed on the weekly telephone calls of our research group (which includes most of the people in Seattle, along with others who couldn't make it from elsewhere).

I'm sorry to push this back on you, but I do want to be as helpful as possible. If, after reviewing the agenda and any of the talks that you'd like, we can provide more material, I'd be more than happy to do so. Additionally, I'm readily available to come in-person or speak by telephone or webinar. I am very confident that we have the proper expertise and experience within our research group, with a strong and feasible plan in process, and I'd cherish the opportunity to highlight those strengths with you and your scientific colleagues.

With best (if slightly jet-lagged) wishes,

[REDACTED]

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**From:** [REDACTED] [mailto:[REDACTED]@icap.org]  
**Sent:** Tuesday, July 08, 2014 3:16 PM  
**To:** [REDACTED]; [REDACTED]@yale.edu  
**Cc:** [REDACTED]

**Subject:** Moderate drinking RCT and methodological issues

Dear [redacted] and [redacted]

Following up on our recent communications about a possible call to discuss various methodological issues that have been raised with regard to the RCT, I wanted to give you a little status report. I have had the opportunity to discuss the proposal (based on the slides you presented in Amsterdam) with several colleagues who also have a scientific background. We identified various areas, including the specifics of the target population, sample size, research centers, monitoring, compliance, attrition, and other predictable topics where further clarification would be needed. However, [redacted], who attended the RSA meeting was able to offer us some insight into the discussions that were held and it seems that many of the issues have been addressed.

Rather than send you my list of questions, many of which have already apparently been answered, I was hoping that you might be able to share a revised protocol with me that we could review. Also, if you have a note of who attended the RSA symposium and of the discussion, this would be extremely useful. It is the validation from your peers in the research community that is essential to the success of this project and will provide the necessary reassurance to potential funders. Once I have had a chance to review this, we can revisit whether there is still a need convene the planned call.

Please don't hesitate to let me know if you have any further questions or if there is anything you would like to discuss.

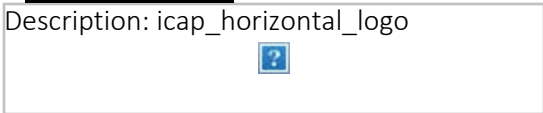
Looking forward to hearing from you,

With kind regards,

[redacted]

[redacted]

[redacted]



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## Methodological issues

We are deeply grateful to GAPG / ICAP for your interest, concern, and insight as we further develop our proposal for a randomized trial of moderate alcohol intake. We respond to individual concerns below and would be happy to discuss any of these issues in more detail where our responses fail to address your primary concerns.

We would like to emphasize one important point, however. Many of these issues will ultimately be decided by a combination of NIAAA (as co-leader of a U01 or similar funding mechanism at NIH) and the final set of investigators. Our responses accurately reflect our efforts to date, which have developed in conjunction with NIAAA, but some of the smaller details will necessarily need to be adjusted based upon both internal and external review at NIH, thus ensuring that the trial is viewed as scientifically valid and unbiased and receives the widest possible attention. Nonetheless, the protocol that we submit to NIH will adhere closely to our suggestions below.

### 1. Outcomes:

The slides include a large number of possible outcomes that could be measured. Will these be prioritized in some way into a few primary outcomes (e.g., CVD, diabetes, all-cause mortality) and possibly some secondary ones that could be derived from subsequent mining of the data?

### Response:

We will follow the general strategy used in most clinical trials. In such trials, a single or two co-primary outcomes are specified, along with several secondary outcomes related to the primary outcome and one or more safety outcomes. For example, in the very large number of trials of new anticoagulants for acute coronary syndrome or atrial fibrillation, the primary outcome might be cardiovascular mortality, the secondary outcomes might include myocardial infarction or total mortality, and the safety outcomes would include major and minor bleeding.

We will use a similar strategy. Our co-primary outcomes are 1) incident cardiovascular disease, defined as non-fatal myocardial infarction, non-fatal ischemic stroke, coronary or carotid revascularization, or cardiovascular mortality, and 2) incident diabetes. Secondary outcomes include total mortality, 'hard' cardiovascular disease (excluding revascularization), and coronary heart disease (excluding stroke and carotid disease) - these are intended to demonstrate the robustness of the primary outcome. Safety outcomes will include cancer, trauma / injuries, all-cause hospitalization, and progression to excessive alcohol use. In conjunction with NIAAA, we will identify an independent data safety and monitoring board, which will ultimately have responsibility for identifying stopping rules, but we will recommend to the DSMB that stopping rules appropriately consider the severity of the outcome, so that, for example, we do not stop the trial early just because a significant benefit for alcohol in incident diabetes occurs, precluding further evaluation of cardiovascular disease.

As with any large randomized trial, once the primary outcomes are reported, several and often dozens of papers appear, either on other outcomes (e.g., change in cognition, change in weight, risk of congestive heart failure) or in interesting subgroups (e.g., risk of cardiovascular disease among diabetic participants). This ensures that the primary paper includes the primary outcomes and receives appropriate emphasis, while taking full advantage of the enormous effort that goes into completion of a clinical trial to produce a much richer body of science.

## 2. Target population:

Is there an upper age limit cutoff? Narrowing the age band would give a tighter cohort. Is this worth doing?

Is the sample intended to be nationally representative in each case, or is the focus specifically on at-risk groups?

How will you control for other predisposing factors (e.g., family history), and also for socioeconomic and demographic variables that could influence the outcomes of drinking?

### Response:

There is inevitably a trade-off when creating more stringent entry criteria, reducing the sample size (or prolonging enrollment) to gain a more homogeneous sample. In this case, excluding older individuals also excludes those at highest risk for events (who are desirable in a study like this). Nonetheless, because initiation of alcohol consumption in very old individuals is apt to be poorly received, we currently anticipate recruiting individuals 50-75 years of age, recognizing that few individuals near 80 are likely to comply with daily drinking.

We do not intend to enroll a nationally representative sample as that term is used epidemiologically (i.e., where the proportions of enrolled individuals can be tied back to the US population), although we do intend to enroll a geographically diverse sample that includes representative numbers of minorities and women; those are requirements of US participants in NIH-funded trials and hence we do intend to enroll a broad and diverse population within the US. By including individuals globally (and we now have collaborators identified in St. Petersburg and Hong Kong), we further ensure generalizability of our findings for policymakers such as the WHO.

At the same time, we will focus on individuals at higher cardiovascular risk, as has been done in most trials of primary cardiovascular prevention (whether of lifestyle or pharmacological therapy). Highly influential trials like PREDIMED (of Mediterranean diet) or JUPITER (of rosuvastatin) focused upon higher risk individuals for several reasons. First, the higher risk of cardiovascular disease in such individuals allows for a smaller sample size; a comparable trial in low-risk individuals might well need to exceed 40,000 individuals. Second, the higher risk also ensures events occur sooner, so that the trial need not exceed 5 years. Third, a focus on individuals at higher cardiovascular risk tends to mimic the population of patients for whom questions about the benefits of alcohol consumption are most salient. That is, we intend to focus on those patients in whom the likelihood of benefit (and, usefully, the desire to remain

adherent) is greatest, maximizing chances for benefit while minimizing risk, exactly as individual clinicians are likely to do.

The advantage of a large randomized trial is that the randomization itself controls for, at least in theory, ALL factors that differ across individuals, including factors we have not yet even identified. Therefore, our primary method of controlling for predisposing factors is randomization. Fortunately, there are also statistical methods (e.g., multivariable proportional hazards regression) that allow us to adjust statistically if, by chance, they are not evenly distributed across the two groups. As with most such trials, the baseline evaluation is typically the most extensive of the entire study, ensuring that we have detailed information on each group for which to adjust. In addition, that information will allow us to conduct subgroup analyses, in which we evaluate whether the effect of alcohol intake is greater among certain types of individuals. Although such analyses must be performed cautiously (because an almost unlimited number could be performed), we will particularly focus on evaluating the consistency of the effect of alcohol across groups defined by factors known to influence cardiovascular disease (i.e., cardiovascular risk factors) or alcohol use (e.g., sex, age).

We will employ centrally-determined randomization with permuted blocks that ensure each site has comparable numbers of individuals in each arm and that random imbalances do not skew our results. In addition, we have explored adaptive designs that allow flexibility in recruitment to ensure adequate numbers of individuals in primary demographic groups and that reduce the final sample if event rates exceed expectation.

### **3. Sample size:**

The total sample size is 10-20,000 individuals over 13 sites, which, in the best case scenario, allows only for about 1500 per site (750 per group), not taking into account attrition. This is a very small sample size.

Would it be worth reducing the number of sites (e.g., 6) and increasing the cohort size in each?

#### **Response:**

It is the total study sample size that determines the power of the study, not the number of sites nor the number of individuals per site (as we propose individual and not cluster randomization). As a result, the effective sample size remains the same, whether we recruit 10 individuals from 1000 sites or 1000 individuals from 10 sites.

There are important reasons not to limit to a very small number of sites, and indeed many trials in the last several years have used the opposite approach (recruiting from literally hundreds or thousands of individual offices). First, it is not feasible to recruit thousands of individuals from a single site in the time period of this study, and recruitment is inevitably a key rate-limiting step. Second, a smaller number of sites would result in less generalizability (i.e., would necessarily not include participants worldwide). Third, it poses a risk of more bias, because problems at a single site would factor more heavily and could ruin an entire trial.

For these reasons, our preference is to expand beyond 13 sites, although still within conservative limits. The conduct of the study itself will ideally occur at a larger number, albeit with at least 250 individuals at each site to ensure a manageable number of sites, such that the total would likely run closer to 25. That ensures a trial that remains easy to monitor but large enough to enroll on time.

#### **4. Adherence**

How likely is it that subjects will adhere to the regimen and the trial groups over several years? An alternative might be to run a pilot and assess likely compliance.

#### **Response:**

We believe that, with appropriate screening and evaluation, adherence (and retention) should be high, although we will certainly maximize this in several ways. This belief is borne out by our experience with dozens of clinical trials of a host of interventions, including physical activity, dietary change, and pharmacological therapies. For example, our collaborator [REDACTED], who has led trials across the US, has studied an intensive lifestyle intervention in LOOK AHEAD and a focused physical activity for elders in the LIFE Trial with clear evidence of adherence – typically 80% of participants achieve high levels of adherence, with variable adherence among the remainder. Similarly, our collaborators from PREDIMED and the Women's Health Initiative demonstrably altered individual's entire diets over several years.

Existing experience in alcohol supports this view. Smaller trials in the range of months to years have now been conducted with alcohol, with proven effects on biomarkers such as HDL-cholesterol of the expected magnitude and direction. Thus, both the published experience with alcohol and the much larger experience in clinical trials suggest that, with sufficiently intense monitoring and feedback, adherence should be more than acceptable. In this case, we plan repeated study visits and frequent study contact (by telephone, email, or web-based methods, based upon local resources) to ensure that participants remain motivated and excited. We will also have a washout period to ensure a common baseline for all participants; this will further serve as a run-in to exclude individuals unable to abstain from alcohol. Further, our power calculations (described further below) already include estimates of adherence.

It is important to note that we anticipate a biological effect of alcohol at a lower dose than that chosen. That is, the bulk of the epidemiological evidence suggests that even intake 3-4 days per week is likely to be beneficial. As a result, adherence in the alcohol arm need not be perfect to demonstrate benefit and even 50% adherence might yield a full result. Because we anticipate less-than-full adherence and because a recommendation for daily drinking is easiest to implement, our intervention includes 7 drinks weekly, thus giving us a wide margin of potential effectiveness.

#### **5. Retention**

Attrition over 5 years is likely to be high. How can this be addressed? For example, by increasing individual cohort size?

**Response:**

Attrition is a very important limitation, and one that experienced trialists take great pains to avoid. We will only use experienced clinical trial sites specifically to ensure that they have demonstrated an ability to retain participants. Our sample size overall also reflects the degree of attrition seen in large clinical trials of lifestyle. However, attrition will not necessarily be high. In the Dietary Modification arm of the Women's Health Initiative, for example, which required wholesale dietary changes to reduce dietary fat and most closely approximates this trial, nearly 49,000 women were randomized and ~2,000 women were lost to follow-up or withdrew (i.e., ~4%).

To address these issues more explicitly, it is useful to review our proposed power calculations. In these, we test a variety of scenarios, some intentionally conservative, to ensure that our sample size needs will be met. We make the following assumptions: 1) a multi-center individually randomized controlled trial; 2) subject enrollment during 3 years (see below) for at least 5 years of follow-up; 3) our primary statistical measure will be a log-rank test of survival curves free of the primary endpoint; 4) the relative risk for the intervention is in the range of 0.7-0.8; 5) possible scenarios of loss to follow-up of 0%, 1%, 3% or 5%; 6) a 5-year risk of developing diabetes of 8.2%; 7) a 5-year risk of CVD of 5.0% (annual incidence rate is 0.0103); and 8) scenarios of true non-adherence (i.e., non-adherence to the point of no effect) of 0%, 5%, 10%, 12.5% or 20%. Within these scenarios, the estimated sample size requirement ranges from ~2,500-12,500 for diabetes and ~4,500-20,000 for CVD, even with the most conservative assumptions. Thus, our estimated sample size (10-20,000, as noted) should account for both lack of perfect adherence and attrition.

**6. Monitoring**

How will monitoring be conducted? What are some of the biomarkers that will be measured and how confident are you that they will accurately be able to reflect drinking levels and patterns?

**Response:**

Monitoring in a clinical trial like this takes many forms. As noted, participants will be contacted repeatedly electronically, using varying approaches to ensure that they remain novel and capture participants' attention, independent of study visits. In-person visits will be most frequent early in the study, when adherence is most challenging. We will conduct timeline followbacks to capture drinking that occurs beyond participant-specific limits (i.e., one drink daily in the intervention arm and any drinking in the control arm), a gold-standard method of evaluation of alcohol use. We are adapting web-based methods to ensure easy and reliable data capture for participants and investigators between visits. Thus, we will have ample information on individual participant's drinking habits using standard clinical methods, and these will form our primary basis for monitoring the safety and adherence of participants.

Biomarkers are attractive methods to supplement clinical interviews, although no biomarker appears to be perfect in assessing adherence to moderate drinking, and we have serious concerns about relying extensively upon them for monitoring. For alcohol, existing biomarkers

have been designed to capture heavy drinking, and the level of intake recommended here will alter them variably. More generally, biomarkers are not commonly used in clinical trials to alter participant behavior. That is, process measures (such as timeline followbacks) are used to improve adherence, while biomarkers are used as secondary outcome measures. As an example, bottle openings might be used to capture adherence to medication, while change in biomarkers like blood pressure or cholesterol would be used as secondary outcomes.

As such, we will measure a variety of biomarkers, some to detect complications of drinking (e.g., GGT, AST, CDT) and others to follow adherence (e.g., HDL-C, ethyl glucuronides, tartaric acid). We believe that some of these (e.g., ethyl glucuronides) should provide useful population-level discrimination between those who drink and those who don't, although they are unlikely to capture exact amounts of drinking and will be of at best uncertain value for individuals. We are working with our partners to evaluate additional biomarkers (e.g., metabolites of hops for beer use) and will add those during the trial if they appear to work well. Because these biomarkers will be used to supplement much more nuanced clinical interviews, however, they need not discriminate perfectly to offer a valuable addition. Furthermore, they will be useful from a publication standpoint to show that the groups differ, even if they are less useful for monitoring individual participants.

#### **7. Beverage variation**

Given that beer and spirits have different alcohol contents, and that beers vary in strength, how will you ensure that these variations do not influence the strength of the effect.

#### **Response:**

This is a somewhat complex issue that bears on the question of what the intervention itself is. Several factors bear on our approach. First, the differences in alcohol content between beverages, while real, are much, much smaller than the difference between drinking and non-drinking. As a result, the two groups will differ meaningfully in their ethanol intake, regardless of what beverage is used. That reflects current clinical practice, in which physicians ask individuals about their servings of alcohol but rarely query the type or strength of that serving. Second, we have found few consistent differences across beverages in their effect on heart disease or diabetes. This suggests that the small differences in alcohol content are indeed modest relative to the similarities across beverages. Third, the key question to consider is what intervention we aim to test. To our group, the intervention is "a daily drink of alcohol", recognizing that it will be operationalized differently by different individuals at different times. Ultimately, the intervention we will test will represent the blended average of all of the types and strengths of alcohol, reflecting the best epidemiological evidence and providing the most useful information to clinicians who might recommend alcohol.

With that said, we will provide repeated, standardized information on portion sizes to attempt to minimize heterogeneity in actual ethanol intake and carefully collect information on the type of beverage (including its alcohol by volume) monthly. With that information, we can, at the end of the trial, examine the 'actual' ethanol intake (i.e., reported frequency of use x the

participant-specific alcohol average) of each participant and relate that to outcomes. We anticipate that the variability across all drinkers will still be far less than the difference between drinkers and non-drinkers, but our analyses will allow us (within the limits of the observed variability) to estimate 'dose-response' curves for our primary outcomes.

#### **8. Incentives**

What incentives will be offered to individuals being encouraged to abstain from drinking? Is it only advice? If so, what kind of advice?

#### **Response:**

All participants will receive generic health advice, typical for long-term clinical trials (e.g., information on a healthy diet, smoking cessation, etc.), along with periodic health examinations and regular attention; experience demonstrates that these are key factors in ensuring adherence and retention. Individuals in the abstinence arm will receive modest monetary compensation, similar to (but likely less than) the cost of alcohol in the other arm. For ethical reasons, it is important to ensure that individuals receive similar compensation in both arms.

#### **9. Feasibility study**

Would it be useful to consider a feasibility study for a year to iron out some of the issues before launching into the full 5-year study?

#### **Response:**

In essence, all of the previous experience of our team represents a vast storehouse of feasibility studies; we have included the leaders of some of the most difficult, complex clinical trials ever conducted. Nonetheless, we recognize the difficulties inherent in any clinical trial. Rather than a separate feasibility study, our preferred approach mimics that of the Women's Health Initiative (a much larger and much more complex trial). We will establish a small number of vanguard sites, chosen for their experience, generalizability, and ability to scale up quickly. These will represent 'beta' test sites, where the trial will be implemented but can be altered and updated to reflect actual trial conduct. In the unlikely event that these sites indicate that the trial is simply not feasible, we will have the opportunity to end the experiment quickly, ensuring savings of resources, time, and effort to NIH, funders, and investigators. This has the very large advantage, however, of using the data from the vanguard sites if the trial is indeed feasible, so that no time or (worse) data are wasted, and ensuring that other sites can be added expeditiously. This approach helps to ensure that the full trial can be completed in the original time allotment (and within budget). As noted above, our sample size calculations reflect this approach, with stepped entry of sites into the recruitment phase over three years as we gain insight from our initial set of vanguard sites.

**From:** [redacted]  
**To:** [redacted] <[redacted]@carlsberg.com>; [redacted] <[redacted]@carlsberg.com>; [redacted] <[redacted]@pernod-ricard.com>; [redacted] <[redacted]@beamsuntory.com>; [redacted] <[redacted]@sabmiller.com>; [redacted] <[redacted]@diageo.com>; [redacted] <[redacted]@molsoncoors.com>; [redacted] <[redacted]@lionco.com>; [redacted] <[redacted]@bacardi.com>; [redacted] <[redacted]@b-f.com>; [redacted] <[redacted]@sabmiller.com>; [redacted] <[redacted]@diageo.com>; [redacted] <[redacted]@B-F.COM>; [redacted] <[redacted]@pernod-ricard.com>; [redacted] <[redacted]@suntory.co.jp>; [redacted] <[redacted]@gapg.org>; [redacted] <[redacted]@gmail.com>; [redacted] <[redacted]@heineken.com>; [redacted] <[redacted]@ab-inbev.com>; [redacted] <[redacted]@ab-inbev.com>; [redacted] <[redacted]@molsoncoors.com>; [redacted] <[redacted]@heineken.com>; [redacted] <[redacted]@bacardi.com>; [redacted] <[redacted]@asahibeer.co.jp>; [redacted] <[redacted]@asahigroup-holdings.com>; [redacted] <[redacted]@kirin.co.jp>; [redacted] <[redacted] (NIH/NIAAA) [C]>; [redacted] <[redacted] (NIH/NIAAA) [E]>; [redacted] <[redacted]@bidmc.harvard.edu>; [redacted] <[redacted]@Diageo.com>; [redacted] <[redacted]@b-f.com>; [redacted] <[redacted]@MOLSONCOORS.COM>; [redacted] <[redacted] Assistant>; [redacted] <[redacted]@kirin.co.jp>; [redacted] <[redacted] s Assistant>; [redacted] <[redacted]@pernod-ricard.com>; [redacted] <[redacted] Asst.>; [redacted] <[redacted]@carlsberg.com>; [redacted] <[redacted]@b-f.com>; [redacted] <[redacted] s Asst.>; [redacted] <[redacted]@molsoncoors.com>; [redacted] <[redacted] Asst.>; [redacted] <[redacted]@sabmiller.com>; [redacted] <[redacted]@diageo.com>; [redacted] <[redacted]@sabmiller.com>; [redacted] <[redacted] Asst.>; [redacted] <[redacted]@Bacardi.com>; [redacted] <[redacted] Asst.>; [redacted] <[redacted]@heineken.com>; [redacted] <[redacted] Asst.>; [redacted] <[redacted]@diageo.com>; [redacted] <[redacted]@heineken.com>; [redacted] <[redacted] Asst.>; [redacted] <[redacted]@ab-inbev.com>; [redacted] <[redacted] (NIH/NIAAA) [E]>

**Subject:** Clinical trial on moderate alcohol consumption - conference call  
**Start:** Monday, December 8, 2014 9:00:00 AM  
**End:** Monday, December 8, 2014 10:00:00 AM  
**Attachments:** [ICAP Conference Call Instructions for participants.pdf](#)  
[ATT06770\\_1.jpg](#)

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Dear All,

The date and time for this call will be on Monday, 8 December at 9am EST, 2pm GMT, 3pm CET, 7am MST and 11pm JST.

Please see attached dial-in instructions for the call.

Kind regards,

[redacted]  
<<ATT06770\_1.jpg>>  
[redacted] (office)  
[redacted] (mobile)  
Email: [redacted]@icap.org



**From:** [REDACTED]  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@bidmc.harvard.edu; [REDACTED]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Progressing the moderate drinking trial  
**Date:** Wednesday, November 19, 2014 12:18:41 PM

---

Sure I will copy you all on the message and calendar invite that I send out to the board to confirm this call which would have the dial-in details attached.

Thanks,

[REDACTED]  
[REDACTED]



[REDACTED] (office)  
[REDACTED] (mobile)  
Email: [REDACTED]@icap.org

---

**From:** [REDACTED] (NIH/NIAAA) [E] [mailto:[REDACTED]@willco.niaaa.nih.gov]  
**Sent:** Wednesday, November 19, 2014 11:01 AM  
**To:** [REDACTED]; [REDACTED]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@bidmc.harvard.edu; [REDACTED]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Progressing the moderate drinking trial

We could do 9AM on December 8. We would need a call –in number for the U.S. and Europe.

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**From:** [REDACTED] [REDACTED]@icap.org  
**Sent:** Wednesday, November 19, 2014 10:22 AM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@bidmc.harvard.edu; [REDACTED]  
**Subject:** RE: Progressing the moderate drinking trial

Dear [REDACTED],

Please see dates and times below and let me know if either of these work best for you all.

Monday, 8 December at 9am EST, 2pm GMT, 3pm CET, 7am MST and 11pm JST

Wednesday, 10 December at 9am EST, 2pm GMT, 3pm CET, 7am MST and 11pm JST

Thanks,

[REDACTED]  
[REDACTED]

[REDACTED] (office)  
[REDACTED] (mobile)  
Email: [REDACTED]@icap.org

---

**From:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@willco.niaaa.nih.gov]  
**Sent:** Wednesday, November 19, 2014 10:09 AM  
**To:** [REDACTED]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@bidmc.harvard.edu; [REDACTED]  
[REDACTED]  
**Subject:** RE: Progressing the moderate drinking trial

[REDACTED]:

[REDACTED] and I would be happy to be on the call, but that week is proving difficult for us. I will be in Paris until the 11<sup>th</sup> (at the OECD meeting) and [REDACTED] will be speaking at the American College of Neuropsychopharmacology Meeting in Phoenix. On Friday, 12/12, we have a meeting with [REDACTED] and [REDACTED] about their potential support for this project .

It is possible I could join in from Paris and [REDACTED] from Phoenix depending on what day and time the call is scheduled. Do you have some options?

[REDACTED]

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**From:** [REDACTED]@icap.org]  
**Sent:** Tuesday, November 18, 2014 11:36 AM  
**To:** [REDACTED] (NIH/NIAAA) [E]  
**Cc:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED]@bidmc.harvard.edu; [REDACTED]  
**Subject:** RE: Progressing the moderate drinking trial

Dear [REDACTED]

As I explained to you, at our last Board meeting we have provided an update to our members about progress on the proposed randomized control trial of moderate drinking. Some have asked for an opportunity to understand more about the protocol that is currently under development. My colleague, [REDACTED], has been in touch with [REDACTED], who has suggested some dates when he could be available for a conference call.

We wondered whether you or [REDACTED] might want to join that call? Although there are some opportunities earlier, I think it would be likely to be sometime during the week of 8 December. If you let me know, we will set up the call from ICAP.

Best wishes, [REDACTED]

**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED]@bidmc.harvard.edu  
**Cc:** [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: Questions for call  
**Date:** Friday, December 5, 2014 1:25:00 PM

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Sigh...some of these reflect absolutely no grasp of what has already been presented to them. Were they paying attention?

I guess we can talk about all of this at 2:15.

**From:** [REDACTED]@bidmc.harvard.edu [mailto:[REDACTED]@bidmc.harvard.edu]  
**Sent:** Friday, December 05, 2014 12:42 PM  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** FW: Questions for call

FYI. I have a few other notes but looks like these are some issues to review together.

**From:** [REDACTED] [mailto:[REDACTED]@icap.org]  
**Sent:** Thursday, December 04, 2014 9:50 PM  
**To:** [REDACTED]  
**Cc:** [REDACTED]  
**Subject:** Questions for call

Dear [REDACTED]

I hope you are well. As it turns out, I did receive a few questions, predictably late. They are included below.

My suggestion would be to work them into the overview.

Another thought I had was to drive home the point that a decision is needed very soon if this is to happen. Perhaps [REDACTED] can also address this. We need a commitment now.

If you would like to speak before the call, tomorrow afternoon works for me. I can also be available some time this weekend. I hope the suggestions from yesterday were helpful.

Kind regards,

[REDACTED]

Questions received :

Credibility of Project

The Overview states that for maximum credibility a trial must be funded by "governmental bodies, health organizations or similar disinterested parties." Will the large percentage of funding from industry, albeit through an intermediary, reduce the credibility of this study?

Control Aspects

1. Describe the concrete steps to be taken to overcome criticisms that data and conclusions are suspect because usage will be self-reported by participants (i.e., dosage will not actually be controlled by NIAAA).
2. Will participants be expected to sign some form of “contract” agreeing to drink at a certain level (e.g., 1 or 2 drinks/day) or not to drink at all?

### Breast Cancer Risk

1. Will breast cancer be one of the Safety Outcomes measured? When will that data first become publicly available?
2. Are women with a family history of breast cancer to be excluded from the cohort? Would that exclusion conflict with randomization which has been described as the primary method for controlling for predisposing factors? (Methodological Issues memo).

### Timing

Data on primary outcomes (cardiovascular) will not be available until years 9 and 10. Data on Safety Outcomes (which includes breast cancer ) will be available much earlier. Does this gap of upwards of 7 years cause a concern?

### Negative outcomes

If the study provides evidence of some negative impacts of alcohol, how will these results be communicated?

Sent from my T-Mobile 4G LTE Device

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**From:** [REDACTED] (NIH/NIAAA) [E]  
**To:** [REDACTED]@harvard.edu  
**Subject:** Re: for your comments  
**Date:** Thursday, February 26, 2015 7:37:44 PM

---

Thanks. Appreciate the edits.

---

**From:** [REDACTED]@bidmc.harvard.edu [REDACTED]@bidmc.harvard.edu]  
**Sent:** Thursday, February 26, 2015 07:14 PM Eastern Standard Time  
**To:** [REDACTED] (NIH/NIAAA) [E]; [REDACTED] (NIH/NIAAA) [E]  
**Subject:** RE: for your comments

[REDACTED] looks great. If you want to add something about the tax benefit, that's up to you – I have no idea if it's relevant. I made some very minor edits.

[REDACTED] and [REDACTED]

I spoke at length with [REDACTED] today and he made a number of very good points:

- The first year of the study normally has the highest costs. While it is true only the Vanguard sites will be running, much of the ground work for the entire study will need to be completed by the vanguard sites and the Clinical Coordinating Center, even if some sites aren't yet recruiting. This includes finalizing the protocol, all of the human subjects reviews at each of the sites, setting up the web-based databases, data entry forms, and quality monitoring for the entire study, finalizing all of the forms and having them translated; and all of the hiring and training of study staff to ensure standardization. It also includes the purchasing of needed hardware (for example there will be a bio specimen repository, which means purchasing freezers to store the samples). That is, there are fixed, up-front costs that tend to be similar, even when a vanguard model is used.
- If there was less money the first year, it could only be handled by delaying some of the first-year costs, such as using fewer vanguard sites and starting them later, but those costs would then be incurred in years two and three, and inflation could increase them further. It would also delay getting the final hoped-for result.
- It would not be possible to have the number of subjects needed to do the basic trial well at less than the \$10 million per year. This is truly the bare bones costs and the planning group has not "padded" the budget to allow for cuts. In fact, they were hoping that any additional funds raised might be used for ancillary studies related to the central questions of the health benefits (i.e. further genetic studies, etc.). It would not be good for the rigor of the study to be put together piecemeal, and many investigators would then be loath to participate at all, because the funding is not solidified up front. For comparison, the NHLBI Women's Health Initiative randomized trial is estimated to have cost \$625 million, so the \$100 million total cost of this trial is very substantially less despite starting two decades later and involving global sites.
- The plan is to do a futility analysis and safety analysis every six months. This way, if it is determined that we know the answer to the research questions early, the study can be stopped early, saving costs. It also means that if there are insurmountable safety issues it would be ended early. There is no guarantee of early closure, but it does mean that the study will only expend costs for as long as scientifically necessary.
- One of the important findings will be showing that moderate drinking is safe. Small studies pose a serious risk of spurious results, including showing harm simply because of bad luck. As we discussed, this will be the first RCT (i.e. "gold standard") evidence of this and it is important to answer statements made by WHO and others that "no level of alcohol is safe" with certainty.

██████████ is willing to discuss all of the above with you and any of your partners, should you want to do that.

I will end by reiterating what ██████████ said in our meeting today that, given the competing priorities of NIAAA and the other NIH Institutes that are joining us, we could not do this trial without industry partnership. It is an important question that comes up every time a new epidemiological paper is published. We really appreciate your work in getting the producers together and continuing to get the answers to their questions. I will send the promised timeline to you by Monday.

It was good to see you and to finally meet ██████████

Take care,

---

**From:** ██████████ (NIH/NIAAA) [E]; ██████████@willco.niaaa.nih.gov]

**Sent:** Thursday, February 26, 2015 5:58 PM

**To:** ██████████ (NIH/NIAAA) [E]; ██████████

**Subject:** for your comments

Let me know what you think and I will send to them ASAP.

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This message is intended for the use of the person(s) to whom it may be addressed. It may contain information that is privileged, confidential, or otherwise protected from disclosure under applicable law. If you are not the intended recipient, any dissemination, distribution, copying, or use of this information is prohibited. If you have received this message in error, please permanently delete it and immediately notify the sender. Thank you.

## Appendix Item F

Synopsis of comments from Michael S. Lauer, MD, Deputy Director for Extramural Research, NIH (former Director of the NHLBI Division of Cardiovascular Sciences) and Barry S. Kramer, MD, Director of the Division of Cancer Prevention at the National Cancer Institute

Michael S. Lauer, MD, Deputy Director for Extramural Research, NIH

- The MACH trial as designed may not be credible from scientific and public health perspectives because:
  - It is based on a difficult-to-ascertain intervention
  - It is based on a problematic composite endpoint
  - It ignores the most recent science on the association between alcohol intake and cardiovascular health
  - It is inadequately powered to assess long-term safety and global health status
  
- I am reminded of Surgeon-General Adams' comments that a proper assessment of "medical marijuana" would involve rigorous drug purification and manufacture, quality control, and accurate measurable dosing. None of that is happening here.
- The composite endpoint includes first occurrence of a non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for angina, coronary/carotid revascularization, or all-cause mortality. Composite endpoints are reasonable if we think a priori that each component will tend to respond to the treatment in a similar way. Yet, as nicely documented in a recent individual-subject analysis of nearly 600,00 current drinkers, increasing alcohol consumption is associated with
  - lower rates of non-fatal myocardial infarction
  - higher rates of non-fatal stroke
  - equivalent rates of cardiovascular disease excluding myocardial infarction
  - higher rates of all-cause mortality
- The authors of that meta-analysis argue that "It has shown that the association between alcohol consumption and total cardiovascular disease risk comprises several distinct and opposite dose–response curves, rather than a single J-shaped association."
- The composite endpoint does not include heart failure, a serious shortcoming. Alcohol consumption is associated with higher risk of heart failure; there is even a well-described "alcoholic cardiomyopathy."
- The meta-analysis also finds increased mortality risk at doses of 100 g/week. The MACH trial calls for doses of 98 g/week. Hence even a slight error in dosing might be expected to cause increased mortality risk.
- A recent Mendelian randomization study suggests that lower levels of alcohol consumption, even starting at moderate levels, is associated with lower (not higher) risk of cardiovascular events.
- The trial is too small (and the intervention too imprecise) to answer an overarching question about the ability of alcohol in moderate doses to improve health. There is

extensive literature showing that increasing levels of alcohol consumption, even at low to moderate doses, increases risk of cancer, liver disease, addiction, hypertension, and motor-vehicle injuries / fatalities. These are illnesses that may be greater immediate risks to middle-aged and young-old adults than cardiovascular disease.

Barry S. Kramer, MD, Director of the Division of Cancer Prevention at the National Cancer Institute

- The study cuts across many endpoints yet it appears there wasn't much consultation across relevant institutes.
- Everyone agrees that when it comes to cancer, alcohol causes harm, yet as far as I know NCI was not consulted.
- The idea of conducting an alcohol RCT is not inherently unethical – there is an element of equipoise. The authors of the recent Lancet meta-analysis say this.
- I would not recommend this study as designed
  - There are not enough patients and not enough follow-up time to allow for meaningful assessment of cancer endpoints, but designed, the trial is set to show the benefit while missing the harm
  - I'm not convinced that this is feasible
  - Huge cost for limited yield
  - The grant as written suggests that the authors do not have equipoise



# NIAAA RFA/PA/RFP Planning and Clearance Process

The clearance process for all NIAAA Requests for Applications (RFAs), Program Announcements (PAs), and Request for Proposals (RFP) begins in the NIAAA Office of Extramural Activities (OEA). Draft RFAs and PAs should be sent to OEA for review prior to formal review and approval by the Research Strategies Committee (RSC). This does not preclude informal discussions within NIAAA beforehand. The process is simply intended to allow for coordination and to assure completeness of the document before formal approval is requested.

RFAs and PAs should address the relevance of research initiatives to the long-term goals of the Institute, as described in the:

- NIAAA strategic plan,
- the health disparities plan,
- the Congressional budget,
- or specific council recommendations.

Council Concept Clearance for new initiatives: The NIAAA Advisory Council is responsible for the high-level review of possible future funding opportunity announcements (grants, cooperative agreements and contracts). The concepts, ideas, and statement of work are presented for Council review and clearance during the Council's open session meetings. Council members evaluate the basic purpose, scope, and objectives of the projects and establishes relevance, priority, and need to accomplish NIAAA/NIH objectives. After the Advisory Council's review, the funding opportunity announcements are drafted incorporating the its suggestions and recommendations.

RFAs and PAs must reflect the strategy developed through the Institute planning process, in terms of Institute priorities, funding levels, and timing of their implementation (i.e., fiscal year). RFAs and PAs may not be submitted without concurrence from OEA. Coordination within NIAAA is particularly important for RFAs, because:

- RFAs entail an obligation of budgetary resources;
- RFAs involve a commitment of personnel resources in order to achieve a rigorous, fair, and scientifically competent review; and
- RFAs require planning to accomplish the review within the time constraints of the announcement.

When the RFA or PA has been put in the appropriate template (including all required boilerplate language) and finalized by program staff, and reviewed electronically by the OEA Director, or in his/her absence, the Chief of the Review Branch or the Chief of the Grants Management Branch or Contracts Branch, the complete RFA/PA must be submitted to the RSC for approval and clearance. If approved, the RFA is forwarded to OEA for administrative review and posting in the NIH Funding Opportunity Announcements Module (FOAM) per FOAM guidelines.

## Appendix Item H

### **Description and Scope of Duties of the Members of the National Advisory Council on Alcohol Abuse and Alcoholism**

The Advisory Council will advise, assist, consult with, and make recommendations to the Director of the National Institute on Alcohol Abuse and Alcoholism, and the Secretary of the Department of Health and Human Services. The Council conducts the second level of review of grant applications for grants and cooperative agreements for research and training and may recommend approval of applications for projects which show promise of making valuable contributions to human knowledge.

#### **Closed Session:**

The review of NIH grant applications is considered confidential, and the portion of the meeting concerned with their review is not open to the public.

The National Advisory Council is not a study section. The Council is charged with ensuring that the initial review process was conducted fairly and that the conclusions and recommendations of the study section are supported by the written documents, such as the summary statements. In reviewing the summary statement, Council should consider the following:

- Are the comments in the critique appropriate?
- Does the summary statement narrative support the priority score? Did the study section raise substantive issues or are the comments trivial?
- Are the concerns reasonable? If the priority score is very good, the summary statement may contain only minor comments. Some comments in the summary statement are not meant as criticisms but rather as feedback to the investigator for improving the research proposal.

**En Bloc Concurrence:** Council members vote en bloc for each group of applications assigned to a specific Program Class Code (PCC) or a group of applications submitted in response to an RFA, on whether they agree or disagree with the recommendations of the scientific review group (SRG).

For applications reviewed and scored by the SRG (55 and better for grants, and 60 and better for small business grant applications), the Council may:

- Concur with all recommendations of the study section, including the budget and duration of support;
- Concur with the scientific assessment but recommend changes in the budget, duration of support or both.

If the Council disagrees with the recommendation of the SRG for a particular application (e.g., the scores and statement narratives do not match, factual errors in the review, etc.), this application may be taken out of the bloc for further discussion, with the following actions:

- Council may vote to return the application to the SRG for re-review.
- Council may defer the application for the next cycle for more information.

**Out of Bloc Discussion:** Foreign applications are not included in “en bloc concurrence”. Each application must be taken out of the bloc for further discussion and final vote. In the event that Council disagrees

with the SRG's recommendation and assessment of the acceptability of the foreign justification, Council may vote "No" or "Defer" the application to the next Council cycle pending more information.

**Other Votes:** Council Members may agree with the recommendations of the SRG and may still select an application out of the "en bloc concurrence", for further consideration to vote on the following actions:

- High Program Priority (HPP): Council may designate an application as HPP, which indicates that an application should be given additional consideration for funding.
- Low Program Priority (LPP): LPP designation signals low enthusiasm for funding.
- Not recommended for further consideration (NRFC): Council may designate an application as "not recommended for further consideration" (NRFC), if there are serious concerns with human subjects and vertebrate animals' research. NRFC'ed applications may not be considered for funding by the Institute.
- Others (OTH): Council may recommend budget reduction and vote OTH.

**Approval to fund:**

- Council may approve or disapprove, upon the request of the institute, the funding of grant applications, whose PI/PD reached the \$1.0 million direct cost threshold of all NIH-funded and pending grants in a given Council cycle (Special Council Review or SCR).
- Council may approve or disapprove R37 MERIT Extension applications of MERIT Awardees.
- Council may approve or disapprove, upon the request of the institute, funding of a non-scored or non-discussed application.

**Funding Decision:** The IC Director makes the funding decision, depending on the availability of funds.

**MERIT Award Nominations:**

- Council may nominate an R01 application for conversion to R37 (MERIT), based on the recommendation of Program Staff. The IC Director selects from the list of applications nominated by Council for the R37 conversion (MERIT Award).

**Approval (Transfer of funded grant from Domestic to Foreign or from Foreign to another Foreign Institution.**

- Council approval is required before a grant may be transferred to a foreign institution. Program Staff present the justification to Council during the closed session for a vote to approve or disapprove the transfer.

**Appeals of Scientific Review:**

Council may consider an appeal of scientific review of a grant application or cooperative agreement based on the flaws of peer review as follows:

- Evidence of reviewer bias.
- Reviewer conflict of interest.

- Lack of appropriate expertise on the committee.
- Factual error that alters the outcome of review.

Program and Review staff present the appeal to the Council. After reviewing program and review staff's recommendation, Council recommends whether to approve or deny the applicant's appeal.

- If Council denies the appeal, applicant must accept the results of initial peer review.
- If Council approves the appeal, NIAAA sends Council's recommendation to the NIAAA Review Branch or CSR for a re-review. Council may also recommend if the same or different panel may re-review the application.

The decision of the Advisory Council is final and cannot be appealed.

***N.B. A simple majority is required for a motion to be carried out.***

### **Open Session:**

The Open Session is open to the public, and any member of the public, including the press, may attend on a space-available basis. Discussions during the open session may lead to information exchange between Institute staff and Council members and can lead to policy recommendations. It also provides an opportunity for the Council to discuss the Director's Reports, and to provide feedback to NIAAA on the effects of Institute policies, scientific directions and operating procedures. Discussions on the inclusion of women, children and individuals from scientifically and medically underserved populations and communities in programs supported by NIAAA, reports from meetings or workshops, and overarching issues of review policy are also included in the open session agendas. High-level reviews of possible future funding opportunity announcements and contract proposals or concepts are presented in the open session. Issues concerning specific grant applications and other confidential matters must NOT be discussed in the open session. Included in the open session are scientific presentations by the extramural scientists, and other presentations (scientific, policy changes, updates) by NIH Staff, NIAAA Advisory Council Ex-Officio members (DoD and VA). At the end of the open session, a public comment period is available.

# Appendix Item I.

## Notice of NIAAA's Participation in NIAMS's PAR-11-169 "Clinical Trial Planning Cooperative Agreement (U34)"

**Commented [g1]:** (7/5) Assigned Reviewers: CSR/DRR; Henry; Guide Policy! [susan]

**Commented [g2]:** (7/5) Notice will be cross-referenced to PAR-11-169! [susan]

### Notice Number:

**NOT-AA-13-004**

### Key Dates

Release Date: [July 12, 2013](#)

### Related Announcements

[PAR-11-169](#)

### Issued by

National Institute on Alcohol Abuse and Alcoholism ([NIAAA](#))

### Purpose

The purpose of this Notice is to inform potential applicants of the National Institute on Alcohol Abuse and Alcoholism's (NIAAA's) participation, effective immediately, in the Funding Opportunity Announcement (FOA) [PAR-11-169](#) entitled "Clinical Trial Planning Cooperative Agreement (U34)". The following sections of [PAR-11-169](#) have been updated to reflect the participation of NIAAA in this FOA:

## Part 1. Overview Information

### Components of Participating Organizations

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)  
National Institute on Alcohol Abuse and Alcoholism ([NIAAA](#))

### ~~Application Due Date(s)~~

~~July 1, 2011, November 1, 2011, March 1, 2012, July 1, 2012, November 1, 2012, March 1, 2013, July 1, 2013, September 15 (NIAAA Only), November 1, 2013, March 1, 2014, by 5:00 PM local time of applicant organization.~~

**Commented [m3]:** Request to have NIAAA date is removed as per email between [redacted] (NIAAA) and CC, KS (DRR)

### Catalog of Federal Domestic Assistance (CFDA) Number(s)

93.846, 93.273

## Part 2. Section I. Funding Opportunity Description

For this FOA, NIAAA's interest includes:

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This FOA issued invites applications to obtain critical and necessary support in the planning and development of feasible and well-designed multicenter clinical trials focused on the effects of moderate consumption of alcohol (as defined by NIAAA guidelines) on the decreased or increased risk of certain chronic diseases. This FOA is designed to support planning activities in preparation for a full-

scale Phase III multicenter clinical trial, which will require subsequent application via a UM1 or a U10 mechanism. Prospective applicants should however note that funding of a Clinical Trial Planning Grant does not guarantee or imply funding for a subsequent application. ~~Pre-approval from NIAAA will be required for submission of an U34 application, as well as for the subsequent UM1 or U10.~~

**Commented [m4]:** Removed as requested  
**Commented [m5]:**  
**Commented [EB6]:** Action: NIAAA cannot pre-approve applications unless they exceed \$500K. Please revise.

## Part 2. Section IV. Application and Submission Information

The Letter of Intent for applications requesting funding from NIAAA should be emailed to:

[Redacted]  
National Institute on Alcohol Abuse and Alcoholism (NIAAA)  
National Institutes of Health  
[Redacted]  
Rockville MD 20852  
Email: [Redacted]

**Field Code Changed**  
**Formatted:** French (France)

## Part 2. Section V. Application Review Information

### 2. Review and Selection Process

Applications assigned to the NIAAA will be evaluateds for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by the NIAAA. Following initial peer review, recommended applications will receive a second level of review by the NIAAA Advisory Council.

**Commented [SK([7]:** Added " assigned to the NIAAA " Kalman 7/11/13  
**Commented [SK([8]:** Small correction, [Redacted] 7/11/13

## Part 2. Section VII. Agency Contacts

### Scientific/Research Contact(s)

[Redacted]  
Office of the Director  
National Institute on Alcohol Abuse and Alcoholism (NIAAA)  
Telephone: 301-402-0332  
Email: [Redacted]

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### Peer Review Contact(s)

[Redacted]  
National Institute on Alcohol Abuse and Alcoholism (NIAAA)  
Telephone: 301-451-2067  
Email: [Redacted]

### Financial/Grants Management Contact(s)

[Redacted]  
National Institute on Alcohol Abuse and Alcoholism (NIAAA)  
Telephone: [Redacted]  
Email: [Redacted]

All other aspects of this FOA remain unchanged.

**Formatted:** Normal

## Inquiries

Please direct all inquiries to:

[REDACTED]

Office of the Director  
National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Telephone: [REDACTED]

Email: [REDACTED]

## Limited Competition Multi-Site Randomized Controlled Clinical Trial Research Center on Alcohol's Health Effects (U10)

This is a request for "Other than Full and Open Competition" process for PAR-AA-XXX entitled "Clinical Trials in Research on Alcohol's Health Effects. Prospective epidemiological studies consistently relate alcohol consumption within recommended limits (up to two standard drinks daily for men and one for women) with lower risk of cardiovascular disease, ischemic stroke, and Type II diabetes. Small-scale randomized feeding trials have defined plausible mechanisms and pathways to explain this putative benefit. However, sizable controversy about this association remains, either because of the possibility of residual confounding, or misclassification of exposure, and the lack of gold-standard randomized evidence. There is general agreement among investigators, health policy experts, health providers, and consumers that a clinical trial is needed. A Significant Item from the Joint Explanatory Statement on the Consolidated Appropriations Act of 2015 contained the following language:

**Moderate Drinking (NIAAA)** -Numerous epidemiological and basic science studies have demonstrated that moderate drinking can be beneficial to health by reducing risk for coronary artery disease, type 2 diabetes, and rheumatoid arthritis, among others. However, these studies used different protocols or questionnaires, and may be difficult to compare. The agreement encourages NIAAA to undertake a multicenter, multiyear clinical study to clarify the health impact of moderate alcohol consumption.

Responding to this need, in July 2013, NIAAA joined in the funding opportunity announcement (FOA) PAR-11-169, entitled "Clinical Trial Planning Cooperative Agreement (U34). This FOA invited applications to obtain critical and necessary support in the planning and development of feasible and well-designed multi-center clinical trials focused on the risk for chronic diseases resulting from moderate alcohol consumption. Prospective applicants were required to be prepared to submit an application for a full-scale clinical trial after completion of the planning cooperative agreement. This FOA will allow the use of a U10 mechanism for applicants funded under PAR-11-169 to meet that requirement.

A U34 planning Grant was awarded in February 2014 to a group of highly qualified investigators with backgrounds in the conduct of feeding trials of moderate alcohol consumption, other dietary interventions, and medication trials in individuals at high medical risk. The award provided one years' worth of funding to develop a pragmatic RCT design that maximized feasibility, adherence, and applicability to clinical practice across international sites with diverse drinking cultures, patterns,



and beverage preferences. This included developing methods to collect and adjudicate clinical outcomes that reflect the diverse range of diseases and conditions previously associated with moderate drinking; identifying potential clinical sites with established research infrastructure to meet recruitment goals; developing novel, efficient methods of assessing and ensuring participant safety; and developing a biospecimen repository and clinical trial management network that will be able to support such a trial as well as future studies.

It is extremely important not to lose the momentum and progress of the involved U.S. and International investigators from the U34, who in the full scale trial will be responsible for sites (Projects) spread across all continents. The group has shown in past trials in which they participated ability to recruit and retain study subjects utilizing similar types of protocols such as low fat diet interventions and hormone replacement regimens.

The unique team of experts described above are the most qualified to submit an application for a very large, multi-site RCT to address the issues in alcohol's health effects that have been brought up by the media, the public, health providers, the U.S. Congress, and the scientific community.

**Uninterrupted conduct of research studies, including clinical trials.** Loss of continued support for the consortium that has been built via the U34 planning grant would interrupt and endanger the success of the important alcohol research planning that has been completed. In addition, it would be a significant loss of a highly qualified team that has been developed over the years.

While the IC (NIAAA) recognizes and endorses the need for full and open competition, and by preference utilizes open competition in the vast majority of its initiatives, we believe that the investment in infrastructure made by the Institute and the commitment of investigators who took part in the RCT development is an exception. Therefore we request the opportunity to issue the PAR XX-XXX: Multisite Clinical Trials in Research on Alcohol's Health Effects (U10) as a Limited Competition.

**Avoiding effort duplication and impact of delays.** NIAAA has invested resources to design a complex, large scale RCT which needs to be conducted nationally and internationally and would like to maintain the momentum of sustained progress. A regression from this point would cost scientific progress both academically as well as financially. In addition, critical analyses would be delayed, resulting in delays of important information for patients, providers, and the medical research community.

Approve 2015-08-14 Digitally signed by [REDACTED] Do Not Recommend Yes

Action: A limited competition isn't justified for this FOA. Just require the results of the U34 in these applications to make sure all applicants are ready to start the trial upon award. See U34/U01 examples from other ICs.

As many of you are aware, the question of whether or not there are protective benefits from low to moderate consumption of alcohol for cardiovascular disease and diabetes, as well as other health conditions remains controversial.

Several epidemiological studies since the 1970's have consistently shown lower CVD risk and lower overall mortality in those who drink moderately when compared to abstainers and heavy drinkers. This effect remains even after controlling for lifestyle and other risk factors, including data from individuals who abstain as a result of serious illness. Recently, this same protective benefit has been seen for Type 2 Diabetes and there was a short term clinical trial published late last year that seems to confirm this observation. In addition, there is a large and growing body of basic science and human laboratory studies that have identified plausible mechanisms for the observed protective effects. Currently, a number of physicians around the world recommend light drinking to their patients at risk for heart attack and ischemic stroke (i.e. Walter Koroshetz testified before Congress that he advises his patients at risk for ischemic stroke to drink a glass of wine every evening with dinner.)

Nevertheless, controversy remains as there are additional observational studies published from time to time that seem to contradict the protective benefits observed. Most recently, Holmes et al which used Mendelian randomization analysis on a review of previous studies and found that the risk of CVD and mortality increased with any drinking.

There have been a number of calls for an RCT to answer the questions raised in the contradictory findings described. Most recently in ACER (1/15) and by members of the U.S. Congress in significant item in the 2015 appropriations language (which you received before today's meeting).

To do a clinical trial well, and of a magnitude to provide enough power to answer the questions, is very expensive. NIAAA funded a conference grant as well as a U34 planning grant in 2014 to consider the feasibility and logistical issues. Both brought together a number of outstanding investigators from major clinical trials (i.e. SPRINT; PREDIMED) who were very interested in the scientific issues of designing and conducting such a study. NIAAA also contacted other NIH institutes to see if they would join in and interest was expressed by NINDS and NIA who added scientific staff to the U34 planning grant.

The Foundation for the NIH was contacted by NIAAA after staff learned that some companies in the alcohol beverage industry were interested in funding an RCT. They are interested in settling the controversy, despite the risk that the answer may not benefit their product. FNIH has a rigorous two-layer review process before it will consider accepting funds to be used in an NIH study. Dr. Collins has a group composed of himself and three additional IC directors that look at a formal Request for Collaboration, and then the FNIH board of Directors has their own review process. There is a strict policy that funders have total hands off of any potential study design and can have no knowledge or influence of the review and award and grants management process throughout the life of the study. Indeed the funders are aware that if they are involved in any way, the results will not be taken seriously. Precedents for industry funding via the FNIH include a Mars Corporation funded study of chocolate, a Quaker Oats funded clinical trial on breakfast and weight loss, and NFL funded studies on CTE.

NIAAA completed the FNIH review process in summer of 2015 and FNIH proceeded to contact potential donors. They received commitment letters from six global alcohol producers for ten years of funding (\$8 million per year for 10 years) for a long term RCT. It is important to note that FNIH will continue to solicit funds from private companies, including the health insurance industry and others interested in this question. As part of the agreement with FNIH, NIAAA agreed to commit some of its own funds (\$2million per year for 10 years, an amount that is standard for RFA's – clinical trials can run \$6 million per year).

In the fall of 2015, NIAAA issued a program announcement indicating interest in reviewing applications for a U10 clinical trial research center. Recipients of the U34 planning grant applied in December 2015. The review took place at the end of March 2016. The FNIH informed NIAAA in January of the fact that the funds were in their bank account, and we would need to make an award in the first half of 2016 according to the agreement they signed with the donors. The application under discussion is for the first 5 years of funding for the study cores and for the initial nine sites. If all goes well with recruitment and compliance during the vanguard phase (first 9 months), NIAAA will issue a follow up PAR to fund 7 additional sites in order to reach the subject total.

The specific aims of the study are as follows:

- Global, six-year, balanced-design randomized trial, comparing the effects of one standard serving (~14 grams) of alcohol intake daily to abstinence on risk of CVD, diabetes, mortality, and related outcomes among 7,800 adults at above-average cardiovascular risk.
- To maximize feasibility and reflect actual use most closely, the test will be alcohol consumption per se compared to abstinence and thus, will offer participants flexibility in their choice of beverage, while employing novel and intensive yet efficient methods to monitor safety.
- **The Primary Specific Aim of this trial is to determine the effects of 14 gm of alcohol intake daily compared with abstinence on risk of major cardiovascular events or death (myocardial infarction, ischemic stroke, hospitalized angina, need for revascularization, or death) over an average of 6 years of follow-up among 7,800 adults aged  $\geq 50$  years with estimated 10-year CVD risk  $\geq 15\%$  or prevalent CVD  $> 6$  months prior to enrollment.**
- Secondary Aims will test the effects of alcohol on risks of incident diabetes and major cardiovascular events.
- Tertiary Aims will test risks of hard cardiovascular events and progression to impaired fasting glucose.
- Similar to other large randomized trials, we will establish ~16 centers worldwide using a stepped approach, with a 9-month vanguard phase among 7 centers in the US, Europe, Africa, and South America (in this application), followed by a second wave of additional sites to complete enrollment.
- Participants will be monitored for safety in multiple complementary ways, including brief electronic real-time reporting and validated yearly instruments and laboratory measures. There will be a DSMB to monitor the study and advise NIH.
- Team consisting of highly successful groups in the US and Europe to establish clinical, data, and biospecimen coordinating centers.
- Field centers include many of the most experienced clinical trialists anywhere, having worked on very large multi-site global trials including SPRINT – systolic blood pressure, and PREDIMED – Mediterranean diet, studies.

NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND  
ALCOHOLISM  
CLOSED SESSION COUNCIL 2016/04  
REVIEW OF GRANT APPLICATIONS

1866 827 9943; [REDACTED]

Wednesday, April 20, 2016  
1:00-2:00

1:00 PM [REDACTED] Call to Order and Introduction to Closed Meeting – Dr.  
[REDACTED]

1:10 [REDACTED] Review of Confidentiality and Conflict of Interest – Dr.  
[REDACTED]

1:15 [REDACTED] Review of Grant Applications- Dr.  
[REDACTED]

[REDACTED] Office of the Director- Dr.  
[REDACTED]

1-U10-AA025286-01 [REDACTED]  
The Moderate Alcohol and Cardiovascular Health Trial  
(PCC AL M)

2:00 PM Adjourn

Best regards,

[REDACTED]

<NCAA Honorarium Form\_2016\_04 Council\_FINAL.docx><Post COI.pdf>

## **DESCRIPTION OF THE FNIH-NIH REVIEW PROCESS FOR REQUESTS FOR COLLABORATION**

When NIH has a project idea and wants to engage the FNIH, an application and formal review process commences. While this process has evolved over time, in general, the protocol in place for the past few years has included the following:

### **1. Application for FNIH partnership – The Request for Collaboration**

NIH staff from the relevant Institutes and Centers (ICs) with a proposed project to be done in collaboration with FNIH contact the Office of Science Policy (OSP) in the Office of the Director to obtain a Request for Collaboration (RFC) form. This form includes a series of questions to describe: the project and how it fits within NIH's mission and goals; steps already taken to develop the project; timeline and evaluative milestones; budget requirements; and potential sponsors. When this form is complete, it is submitted to OSP to begin the review process.

### **2. Review of Requests for Collaboration (RFC) by the Office of Science Policy**

Proposals from NIH ICs are submitted to OSP for consideration. OSP conducts the first level of proposal review via the OSP FNIH Proposal Review Committee. The OSP Committee consists of four or five NIH staff members with a range of scientific expertise. Each committee member evaluates the proposal independently against set criteria, including the project's fit with NIH's mission and priorities, its benefit to NIH, its uniqueness and ability to leverage resources, and the adequacy of its design. The committee then convenes to discuss the RFC and arrives at a consensus evaluation of the proposal.

### **3. Request for Collaboration Review by NIH-FNIH Steering Committee**

After OSP review, the RFC and a copy of the OSP evaluation form are submitted to the NIH-FNIH Steering Committee. This committee of senior NIH leadership includes representation from the Office of the General Counsel, the NIH Intramural Research Program, IC Directors, and the offices of the Deputy Director for Science, Outreach, and Policy. The Steering Committee reviews the proposal and evaluates the project's suitability for FNIH partnership, informed by the OSP evaluation.

### **4. Request for Collaboration Review by FNIH**

If the NIH-FNIH Steering Committee approves a RFC, then the proposal is submitted to the FNIH. The FNIH then performs its own due diligence in considering the proposal, reaching out to the NIH IC contact person as needed to clarify details of the proposal and contacting potential funders to determine the appetite for the project and the willingness to contribute funds. FNIH staff shares these results with a committee of the FNIH Board of Directors, which decides whether to approve the partnership. If approved, the NIH is informed and the FNIH commences fundraising to support the project, which may take a few months to a few years, depending upon the project funding climate, the nature of the project, and its duration.

Review criteria and principles for collaboration:

#### **Mission-Appropriate**

- Consistent with NIH's mission and aimed at advancing one or more of its goals
- Not involving an organization that has a mission contrary in purpose to NIH or the USG

#### **Value-Added**

- Of clear benefit to NIH and its ICs and meets an unaddressed need
- Non-duplicative of efforts underway at NIH, unless a sufficient justification is given

- Leveraging resources across multiple sectors with synergistic effect

**Practicable**

- Proposal concept is well defined with achievable milestones and a timeline for completion
- Cannot be accomplished by NIH mechanisms (e.g., gift fund)

<https://osp.od.nih.gov/policy-reporting/nih-fnih-public-private-partnerships/>

<https://osp.od.nih.gov/policy-reporting/nih-staff-initiated/>



**REQUEST FOR COLLABORATION  
Public Private Partnership**

1. **Today's Date:** February 20, 2015

**2. Contact Information**

- a. Name, title, and contact information (phone number, e-mail and mailing address) of NIH contact person: [REDACTED]
- b. Primary NIH IC: NIAAA
- c. Other ICs or government agencies already involved in this project: NINDS, NIA

**3. About the Project**

- a. What is the name of the project? Multi-site Randomized Trial of Health Effects of Moderate Drinking
- b. What critical needs is your project addressing? What is the overall clinical/scientific significance of the project?

Prospective epidemiological studies consistently relate alcohol consumption within recommended limits (up to two standard drinks daily for men and one for women) with lower risk of cardiovascular disease, ischemic stroke, and Type II diabetes. Small-scale randomized feeding trials have defined plausible mechanisms and pathways to explain this putative benefit. However, sizable controversy about this association remains, either because of the possibility of residual confounding, or misclassification of exposure, and the lack of gold-standard randomized evidence. Currently, governmental public health entities and scientific/medical societies stop short of recommending that individuals be advised to consider moderate alcohol consumption as part of a healthy lifestyle.

At the same time, health professionals are often asked by their patients, or otherwise ponder, what to do in individual clinical situations where it is possible that moderate



alcohol use might be beneficial. The January, 2015 issue of *Alcohol: Clinical and Experimental Research* is an excellent example of the present debate:

<http://onlinelibrary.wiley.com/enhanced/doi/10.1111/acer.12585/>

<http://onlinelibrary.wiley.com/doi/10.1111/acer.12582/full>

There is general agreement among investigators, health policy experts, health providers, and consumers that a clinical trial is needed. A Significant Item from the Joint Explanatory Statement on the Consolidated Appropriations Act of 2015 contained the following language:

**Moderate Drinking (NIAAA)** -Numerous epidemiological and basic science studies have demonstrated that moderate drinking can be beneficial to health by reducing risk for coronary artery disease, type 2 diabetes, and rheumatoid arthritis, among others. However, these studies used different protocols or questionnaires, and may be difficult to compare. The agreement encourages NIAAA to undertake a multicenter, multiyear clinical study to clarify the health impact of moderate alcohol consumption.

- c. 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?

The primary study objectives are as follows: 1) To determine the effects of one serving of alcohol (approximately 14 grams) daily, compared to no alcohol intake, on the time to incident cardiovascular disease (myocardial infarction, ischemic stroke, cardiovascular death) among adults at above average cardiovascular risk; and 2) To determine the effects of one serving of alcohol (approximately 14 grams) daily, compared to no alcohol intake, on the time to American Diabetes Association-defined incident diabetes among participants free of diabetes at baseline.

The study design will be a randomized, multicenter, international, assessor-blinded, parallel group, balanced clinical trial. We expect to fund 25 to 30 field centers world-wide, an administrative center, a clinical coordinating center, a statistical coordinating center and a biospecimen repository center.

The study population will be adults 50+ years old at above average cardiovascular risk. Subjects will be not alcohol naïve with an AHA/ACC Risk score of >10%.

The enrollment duration will be one to three years at Vanguard sites and two to three years at all sites. We expect to enroll 14,000 randomized participants from the sites with equal numbers in each arm.

d. Describe the project timeline, deliverables and milestones.

- It is anticipated that a limited competition RFA will be released in April of 2015.
- Grant applications will be due in July, 2015
- Review will take place in August/September 2015
- It is anticipated that a grant award will be made early in FY 2016 after Advisory council review.
- The first year will focus on protocol finalization, infrastructure development, DSMB formation and obtaining IRB approval.
- Site start-up for approximately 5-7 Vanguard sites will occur in fall of 2016
- Enrollment for remaining sites will take place in late 2016 through 2017
- Study enrollment to continue through 2019
- Subjects will follow protocol and be monitored for alcohol use and tested every six months for five years or until they reach a study endpoint. This will continue until year 8 (2023).
- Quality control at the site level will be monitored throughout.
- Monthly conference calls/webinars for all sites
- Year 9 will be analysis of data and (2024)
- Year 10 will focus on publication, and scientific presentations (2025)

e. How does this project fit within NIH's mission and goals?

A significant goal from the NIH Mission Statement is as follows, "...the NIH provides leadership and direction to programs designed to improve the health of the Nation by conducting and supporting research: in the causes, diagnosis, prevention, and cure of human diseases; ..."

As stated above, given the controversial nature of alcohol and the evidence from observational studies, a large multi-site, rigorous clinical trial is necessary. The cost of such a study is prohibitive, given competing priorities in alcohol research and current Federal budget limitations. This trial could not be done in the current climate without private funding sources. At the same time, the NIH scientific expertise and leadership is needed to ensure it is implemented to the highest standards, including scientific peer review and Involvement of NIH scientific oversight.

f. 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 people from industry, academic institutions, associations, societies, etc.)

The International Alliance for Responsible Drinking, IARD, has coordinated commitments from six global alcohol producers. The contact individual and her information is below:

[REDACTED]

International Alliance for Responsible Drinking (IARD)

1225 19<sup>th</sup> Street NW, Suite 500

Washington, D.C. 20036, USA

Office: [REDACTED]

Mobile: [REDACTED]

- g. 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. This can include individuals, foundations, businesses, associations, organizations and societies.

There is also interest from the health insurance industry.

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

A U13 conference Grant was awarded in FY 2014 to [REDACTED] Beth Israel Deaconess Medical Center. A conference took place in 6/2014 in conjunction with the annual Research Society on Alcoholism Meeting that brought together alcohol researchers along with experts in related fields to share methodological approaches and suggestions. Participants included experts in the conduct of feeding trials of moderate alcohol consumption, dietary interventions, and medication trials in individuals at high medical risk to identify problems and solutions and begin the process of building a very large scale, long term clinical trial.

A U 34 planning Grant was awarded in February 2014 to the same group that provides 1 years' worth of funding to develop a pragmatic RCT design that maximizes feasibility, adherence, and applicability to clinical practice across international sites with diverse drinking cultures, patterns, and beverage preferences. This includes developing methods to collect and adjudicate clinical outcomes that reflect the diverse range of diseases and conditions previously associated with moderate drinking; identifying potential clinical sites with established research infrastructure to meet recruitment goals; developing novel, efficient methods of assessing and ensuring participant safety; and developing a biospecimen repository and clinical trial management network that will be able to support such a trial as well as future studies.

- i. 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?

There are no current known projects of this scale with the expressed goals outlined in this document.

- j. Does this project include any meetings, conference or symposia?

Although not yet discussed, it is possible that managing this consortia of several research sites over the proposed study period of 10 years, will be enhanced by periodic meetings of study investigators and staff and NIH staff collaborators.

#### 4. What is the anticipated role of the NIH IC in the project?

- a. What are some of the key scientific and/or administrative activities (outputs) for which the NIH IC will be responsible?

NIAAA, in consultation with NINDS and NIA, will publish a limited competition RFA inviting an application for a Project Coordinating Center and research sites.

NIAAA Division of Extramural Affairs, in consultation with NINDS and NIA, will set up and conduct the application review.

This project will use a U mechanism that will, as such, involve NIH scientific staff from the collaborating IC's in active scientific and leadership roles throughout the study, including publications and presentations at scientific conferences. There will be a steering committee comprised of NIH staff, outside experts, and study personnel. The funders will not be included.

The project will involve program and grants management staff for standard NIH grant management procedures.

- b. Are there anticipated funding/grant awards? What are the deadlines for these awards?

Yes. It is anticipated that an award will be made in early FY 2016.

- c. How will your project be publicized?

A notice will be published in the NIH Guide for Grants and Contracts.

#### 5. What specific role are you requesting FNIH to fill? Examples of FNIH activities are listed below.

- i. *NIH-managed projects may include partnership development, convening of key stakeholders, program development, coordination, and/or administration, fund-raising or fund distribution, reporting as required by donors.*
- ii. *FNIH-managed projects may include services above in (i) 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 confidentiality); facilitating scientific collaborations within the project; and the reporting of overall scientific and/or financial activities to the donor(s).*

It is anticipated that FNIH will work with private industry donors to put the contractual agreement in place and serve as the point of contact with NIH on all

matters pertaining to the contract. This includes some aspects of partnership development, coordination, administration, and reporting required by donors.

It is also anticipated that FNIH will provide ongoing financial monitoring and oversight that may be necessary that does not fall under the NIH grants management function.

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

FNIH and NIAAA will work together to insure that the contract is in place and functioning according to donor and NIH policy and satisfaction. FNIH will be expected to coordinate industry contact and make NIAAA staff aware of issues and problems and work together with industry partners to resolve them

- b. 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)?

This will be an ongoing relationship beginning in the spring/summer of 2015, throughout the project period of 10 years – fall of 2025.

## 6. Budget

- a. Please provide as complete a budget as possible, with expenses and timelines. Specifically identify NIH's contributions (both NIH appropriated funds and in-kind support) for the life of this project.

The total cost of the project has been estimated at \$100 million dollars over the 10 year project period. NIAAA will provide \$2 million per year for 10 years. Extramural Scientific Staff from NIAAA (up to 5 individuals) and collaborating IC's (up to 2) will be assigned to the project as staff collaborators over the life of the project. Grants Management staff will perform normal grants management duties.

- b. Please describe the support expected from private partners, including timelines, for the life of this project.

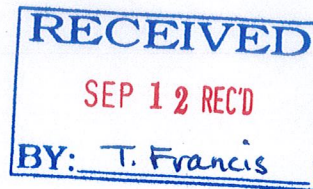
Private partners will provide 80% of the project funds, or \$8 million per year for 10 years. FNIH will work together with industry donors to develop the most efficient plan/timeline for payment of funds to NIH and distribution to NIAAA and grantee, but it is anticipated it will work out to \$8 million per year for 10 years.

**7. Assessment** - 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?

Standard clinical trial success indicators will be monitored. These include study enrollment, retainment, and compliance with protocol. After the trial period, success will be measured in scientific publications and presentations at scientific conferences.

**8. Additional Information** - Please provide any additional information that would assist the FNIH in evaluating this project and determining how we can be most effective.

The funder's role will not go beyond donating the money. It is very important to the industry that they have no involvement in the design or conduct of the trial, in order that there is no question about the findings. They are concerned that there is not even the *appearance* that they influenced the trial in anyway.



Memorandum of Understanding  
Between  
The Foundation for the National Institutes of Health, Inc.  
and  
National Institute on Alcohol Abuse and Alcoholism  
for  
**Multi-Site Randomized Control Trial of Health Effects of Moderate Drinking**

This Memorandum of Understanding (“MOU”) is entered into by and between the National Institute on Alcohol Abuse and Alcoholism (“NIAAA”), an agency of the United States Government, and the Foundation for the National Institutes of Health, Inc. (“FNIH”), a Maryland 501(c)(3) not-for-profit corporation. NIAAA and FNIH are referred to herein individually as a “Party” and collectively as the “Parties”.

WHEREAS, the NIAAA is authorized and established by Title IV, Part C, Subpart 14 of the Public Health Service Act, 42 U.S.C. § 285n to conduct and support biomedical and behavioral research, health services research, research training, and health information dissemination with respect to the prevention of alcohol abuse and the treatment of alcoholism; and

WHEREAS, the NIAAA proposes to establish a study entitled: *“Multi-Site Randomized Control Trial of Health Effects of Moderate Drinking”* (“Project”), a multiyear-year program that aims to determine the effects of moderate alcohol consumption—defined as 14 grams of alcohol daily—and no alcohol intake in a sample of adults, living throughout the world, of sufficient size to provide adequate statistical power to answer the main study questions. Primarily, the Project will measure the effects to: 1) the time to a cardiovascular event (e.g., ischemic stroke, myocardial infarction or cardiovascular death) for adults at above average risk for cardiovascular disease; and 2) the time to incident diabetes, as defined by the American Diabetes Association, for individuals who did not have diabetes at baseline; and

WHEREAS, the FNIH was established by Section 499 of the Public Health Service Act, 42 U.S.C. §290b, to support the National Institutes of Health (“NIH”) in its mission and to advance collaboration with biomedical researchers from universities, industry, and non-profit organizations and is incorporated as a 501(c)(3) not-for-profit corporation; and

WHEREAS, the FNIH desires to assist NIAAA in its efforts by raising funds (“Donations”) from private parties to accomplish the Project.

NOW, THEREFORE, in consideration of the promises and covenants contained herein the Parties agree as follows:

**A. NIAAA Responsibilities**

1. NIAAA will be responsible for managing the programmatic, logistical, and administrative aspects of the Project.
2. NIAAA will ensure the Project is administered in accordance with the laws, regulations and policies generally applicable to NIH and to NIH-funded research, including those intended to preserve the integrity of NIH peer review and award-making processes and those intended to promote objectivity in the design, conduct, and reporting of NIH-funded research. It is understood and agreed that no Donor will have control over the Project. The FNIH’s participation in the Project is predicated on the independence of the study, as indicated in Attachment 1.

3. Once the NIAAA Director approves an Award, NIAAA (or NIH) agrees to promptly, but in no later than five business days, inform the FNIH's Director of Development and Chief Financial Officer in writing of:

- The name(s) and affiliation(s) of the Awardee,
- The timeline for issuance of the Notice of Grant Award ("NoA"),
- The total anticipated amount of funding desired from the FNIH,
- A proposed schedule for the desired payment(s) of the funding amounts, including the desired amount of the first payment,
- The general purposes to which such payment(s) will be put, and
- The date by which NIAAA will complete negotiations of the award.

4. The NIAAA agrees to request early in its communications with the Awardee that under no circumstances shall the Awardee communicate with Donor(s) with regard to the Project without written consent of the FNIH President or an FNIH Contact listed in Section (B)(7).

5. Upon issuance of the NoA, NIAAA agrees to promptly, but in no later than five business days, inform the FNIH's Director of Development and Chief Financial Officer in writing of:

- The final high-level award budget,
- The exact amount of funding requested from the FNIH,
- The CAN number to which funds should be transferred,
- The dates by which funds transfers are desired, it being understood that the first funds transfer shall not be less than 90 days from the date the FNIH is informed or whichever date is stipulated in the relevant Donor agreement.

6. Upon issuance of an NoA or other formal or publically-announced agreement with an Awardee, NIAAA agrees to promptly, but in no later than five business days, inform the FNIH's Director of Development in writing of:

- The name(s) and affiliation(s) of the Awardee,
- Other publically available details and information relevant to the Award such as the name of the Project and Project abstract.

7. Under no circumstances shall NIAAA or its representatives communicate directly with any Donor in order to raise funds for the Project or to disclose to a Donor any information contained in Section (A)(6), it being understood that such communication shall be managed and coordinated by and through the FNIH.

8. NIAAA agrees that it will not communicate directly with any Donor about the Project or funding for the Project without the written consent of the FNIH President or an FNIH Contact listed in Section (B)(7), unless an FNIH representative is included in such communication.

9. NIAAA agrees to promptly, but in no later than five business days, inform the Director of Development if a Donor has communicated directly with NIAAA with regard to the Project without the consent or inclusion of the FNIH. NIAAA agrees to instruct an Awardee to inform NIAAA if a Donor has communicated directly to it without the consent or inclusion of the FNIH and promptly, but in no later than five business days, inform the FNIH.

10. NIAAA agrees to be responsible for any costs it incurs as a result of administering the Project or otherwise in furtherance of the Project, notwithstanding any Donations that FNIH has raised for the Project.



11. NIAAA acknowledges that the FNIH shall, in its sole discretion, establish, apply, and recover its direct and indirect costs and that the FNIH shall negotiate these confidentially, independently, and directly with Donor(s). The FNIH in its sole discretion, may disclose to NIAAA the net amount of funds raised for the Project.

12. NIAAA will be responsible for preparing public communications regarding the Project in accordance with standard NIH and Department of Health and Human Services (“HHS”) clearance requirements and as described in this Section. NIAAA agrees to provide drafts of all such communications, including any communication involving references to FNIH and/or its Donors, to FNIH within 10 business days prior to its public availability or dissemination and will endeavor in good faith to incorporate suggestions by FNIH as appropriate. FNIH acknowledges that NIAAA may disclose details about the Project to third parties at its discretion. Should NIAAA wish to disclose details about the Donors or Donations, NIAAA agrees to consult with the FNIH prior to making such disclosure. NIAAA may acknowledge the FNIH and Donors for their support, including in communications contemporaneous with the release of Project results. The language that NIAAA anticipates using in these instances is:

*“The Project is a collaboration among the National Institutes of Health (NIH) and extramural research sites in the United States and internationally. Funding is provided by NIH, foreign government agencies, non-profit foundations and private sector organizations. Non-profit foundations and private sector organizations providing funding for the Project include: [FNIH may supply a list of Donors and facilitate Donor review prior to dissemination]. NIH had sole responsibility for the selection of the award recipient(s) and for oversight as appropriate of the design and conduct of the Project and for the reporting of the Project results. Funding by non-profit foundations and private sector organizations is managed through the Foundation for the National Institutes of Health (FNIH), a 501(c)(3) not-for-profit organization. Donors did not have any control over the design or conduct of the Project, nor were they provided access to any non-public Project results.”*

13. NIAAA agrees to provide to FNIH, in a timely manner, an annual report of publicly available information, describing the progress, activities, and outcomes of the Project, and information on how funds provided by FNIH have been spent. NIAAA also agrees to provide this information from time to time upon FNIH request.

14. NIAAA contacts for the Project are:

Programmatic Contact

Name: [REDACTED]  
Title: [REDACTED]  
Phone: [REDACTED]  
Email: [REDACTED]

Administrative Contact

Name: [REDACTED]  
Title: [REDACTED]  
Phone: [REDACTED]  
Email: [REDACTED]

Communications Contact

Name: [REDACTED]  
Title: [REDACTED]  
Phone: [REDACTED]  
Email: [REDACTED]

## B. FNIH Responsibilities

1. The FNIH will undertake its best efforts to solicit, receive, manage and acknowledge private Donations for support of the Project and will hold such Donations until it is determined how to spend the funds. As indicated in Attachment 1, FNIH will also commit its best efforts through June 2016 to find additional sources of funds in order to reduce the funding burden on the currently anticipated Donors. If the NIAAA requires additional Donations for the Project after June 2016, the FNIH agrees to extend its best efforts for a period of one year, unless the FNIH notifies NIAAA in writing (which includes by email) that the FNIH will cease fundraising efforts for the Project. The Parties will formally assess funding needs for the Project in 2018.

2. It is anticipated that Donor funding transferred to NIAAA for support of the Project will be awarded by NIAAA using normal NIH funding mechanisms. In limited circumstances and, as requested by NIAAA and with the support and input of NIAAA, the FNIH may be called upon to make and oversee related FNIH grants and/or contracts for ancillary studies or other research with one or more Project study sites.

3. Subject to Section (C)(2) below and in coordination with NIAAA, the FNIH will use the Donation(s) it has received under Section (B)(1), less funds retained to underwrite the FNIH's direct and indirect costs, to support the Project either directly, through contributions to NIAAA's Conditional Gift Fund, or via other authorized transfer mechanisms. The FNIH may do so if NIAAA provides i) 30 days prior written notice that it is requesting such funds, ii) a high-level overview of the use(s) to which it intends to put such funds, and iii) a high-level overview of the use(s) to which it has put funds previously remitted to it under this MOU. If the request is satisfactory to the FNIH, and sufficient funds are available, then the FNIH will either:

- a. Transmit funds as a conditional gift to the specified NIAAA CAN
- b. Transfer funds to NIAAA pursuant to 42 U.S.C. §290b(j)(10)
- c. Fund grants and/or contracts to Project study sites under section (B)(2) above
- d. Pay FNIH's vendors directly.

4. Interactions with Donors shall be managed and coordinated by or through the FNIH throughout the life of the Project including responding to Donors' requests for information. FNIH may provide Donors with an annual programmatic and financial report of the Project, using among other things material provided in Section (A)(5). The study protocol, Project data and other non-public information will not be shared with Donors or any other private-sector organization, including those organizations providing funds for the Project.

5. The FNIH, in consultation with NIAAA, will work to ensure appropriate publicity and recognition for the Donors. However, the FNIH reserves the right to disclose details about the Project to third parties at its discretion. Should the FNIH wish to disclose details about the Project, the FNIH agrees to consult with NIAAA prior to making such disclosure. For purposes of transparency, the FNIH may mention the Project on its website and in its annual report(s), and may include the Donors on a list of the many donors listed in such materials.

6. Upon reasonable request from NIAAA, FNIH agrees to provide NIAAA with a financial report of the funds disbursed by FNIH to support the Project.

7. The FNIH contacts for this Project are:





**C. General Provisions**

1. It is understood and acknowledged by the Parties that NIH employees are prohibited from soliciting gifts; all such activities will be undertaken only by the FNIH pursuant to its statutory authority.
2. Should NIAAA or any Donor(s) request FNIH to perform other related tasks not currently specified in this MOU, the FNIH agrees to consult with NIAAA regarding the costs associated with these tasks. If mutually agreed upon by FNIH, NIAAA and the relevant Donor(s), FNIH also will be reimbursed for its costs for such additional tasks from the Donations received under Section (B)(1).
3. The Parties may revise or modify this MOU by written amendment hereto, provided such revisions and/or modifications are mutually agreed upon and that any such amendment is signed by each Party hereto.
4. The Parties expect the MOU to extend from the date it is executed by both Parties through the end of the Project (“Term”), currently scheduled as December 31, 2026. Either Party may terminate this MOU upon 30 days prior written notice to the other Party.
5. Upon completion of the Project, or in the event this MOU is terminated before completion of the Project, FNIH will retain control of any undisbursed Donations received under Section (B)(1). In accordance with the wishes of the Donor(s) and at the discretion of the FNIH Board of Directors, Donations not spent in furtherance of the Project may be returned to the Donor(s) or used for activities reasonably related to the original purpose of the Donations.
6. This MOU contains the entire agreement of the Parties with respect to the subject matter hereof and supersedes all prior and/or contemporaneous agreements or understandings, written or oral, with respect to the subject matter of this MOU.
7. This MOU shall be construed and interpreted in accordance with the laws of the State of Maryland and Federal Law. In case of a conflict, Federal Law will prevail.
8. This MOU may be executed in counterparts, each of which shall be deemed to be an original and all of which together shall constitute a single document.
9. For purposes of this MOU, “Donor” means a private party who has made a Donation or who may potentially make a Donation, to accomplish the Project, including persons affiliated with such private party such as its staff, directors, officers, contractors, advisors, or collaborators, or other individuals, entities, NIH awardees, past or present scientific colleagues, or those drawing compensation who are

reasonably associated with such private party.

10. For purposes of this MOU, "Awardee" means the institution(s) that is (or are) the recipient(s) of NIAAA funding for this Project, which will be supported in whole or in part by funds raised (or funds that are anticipated to be raised) by the FNIH. Also for purposes of this MOU, the obligations and expectations of the Awardee as designated herein are intended to extend to all individuals and/or entities acting on behalf of the Awardee for purposes of the Project.

*SIGNATURES BEGIN ON NEXT PAGE*

*SIGNATURES*


In Witness Whereof, the Parties have executed this MOU, effective on the latest date of the signatures of the Parties below.

Approved and Accepted for the National Institute on Alcohol Abuse and Alcoholism:

Signature:  Date: 9-7-16

Name: George Koob, Ph.D.  
Title: Director

Approved and Accepted for the Foundation for the National Institutes of Health, Inc.

Signature:  Date: 9-16-16

Name: Maria C. Freire, Ph.D.  
Title: President and Executive Director

JPT  
9/13/16  
KAL  
9/14/16

## Attachment 1 - Letter to NIAAA



July 6, 2015

George Koob, Ph.D.  
Director  
National Institute on Alcohol Abuse and Alcoholism  
5635 Fishers Lane, Room 2001  
Rockville, MD 20852

Dear Dr. Koob:


I am very pleased to let you know that after due diligence and careful consideration, the Foundation for the National Institutes of Health (FNIH) Board of Directors has approved that FNIH work with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and external funders to support the Multi-site Randomized Control Trial of Health Effects of Moderate Drinking. In their decision, the Board understands that the study will be conducted independently from the funders – their support will be only to provide funds. FNIH participation in this project is predicated on this independence of the study.

FNIH has been asked to raise approximately \$80 million from the private sector to support the study over 10 years, and to undertake stewardship activities related to these funds. Our due diligence indicates that sufficient funding is available to meet this goal. We also will commit our best efforts through June 2016 to find additional sources of funds in order to reduce the funding burden on current anticipated donors, as has been requested of us. FNIH's costs relating to these activities will be covered from funds raised.

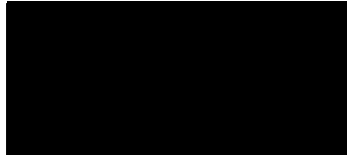
Our staff has been in communication with Drs. [REDACTED] and [REDACTED] during our due diligence and review process and will continue to maintain contact with appropriate NIAAA staff throughout the life of the study.

We look forward to working with you on this very important program.

Best regards,

  
Martin C. Freize, Ph.D.  
President and Executive Director

Cc:



6650 Rockville Pike, Bethesda, MD 20814  
phone 301.402.5311 fax 301.402.2752

Partners for Innovation, Discovery, Health  
[www.fnih.org](http://www.fnih.org)

**Appendix Item L.1.(a)**  
**Analysis of NIH-funded scientific topics: NIAAA 2008-2017**

## Using word2vec to characterize NIH research

### Word2vec

- Computational method that maps words in multidimensional vector space
- Summarizes documents by their semantic content
- Enables clustering of documents based on content similarity
- Used to measure the relatedness of RPG awards from F 2010-F 2017 (81,463 documents)
  - 148 topic clusters

### Cytoscape

- Tool used to display the network of word2vec-defined topic clusters
- Scientific topic nodes are sized by NIH application percentages and heat-mapped by
  - NIH-wide award and application rates
  - NIH-wide topic award rates
  - Fraction of IC award rates over total awards in topic cluster

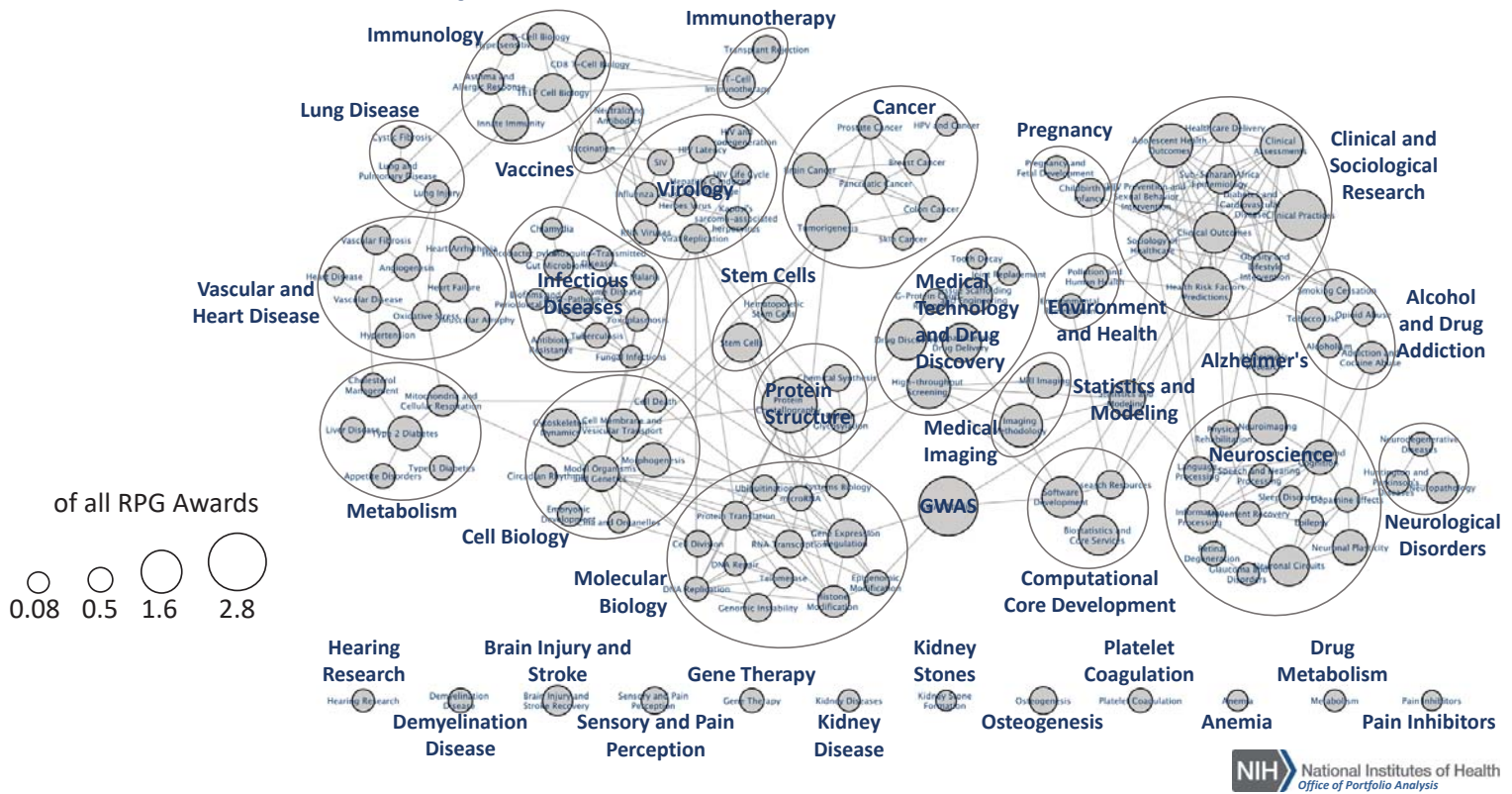
## Using word2vec to characterize NIAAA research

### NIAAA Data Used

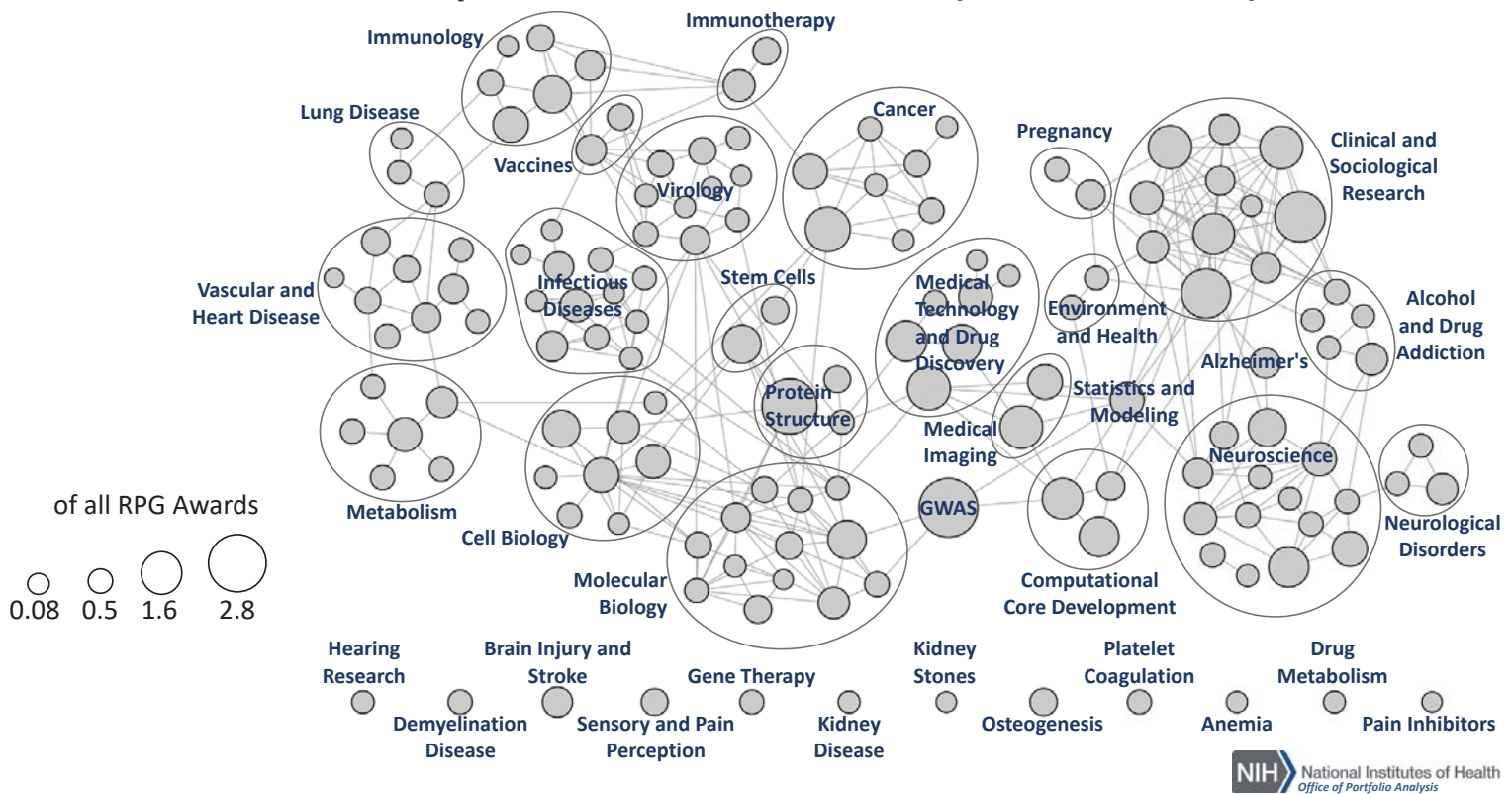
- *iSearch* criteria
  - 2008 -2017
  - Admin IC: NIAAA
  - Awarded Only
  - RPG Only
  - Type 1 and Type 2
- Results: 1,891 applications
- Grouped applications by year and calculated the distribution across the F 10-F 17 RPG cluster map
- Presenting a heat-map colored by the percent of how many NIAAA awards are in each cluster
- Gray clusters indicate no awards in that cluster



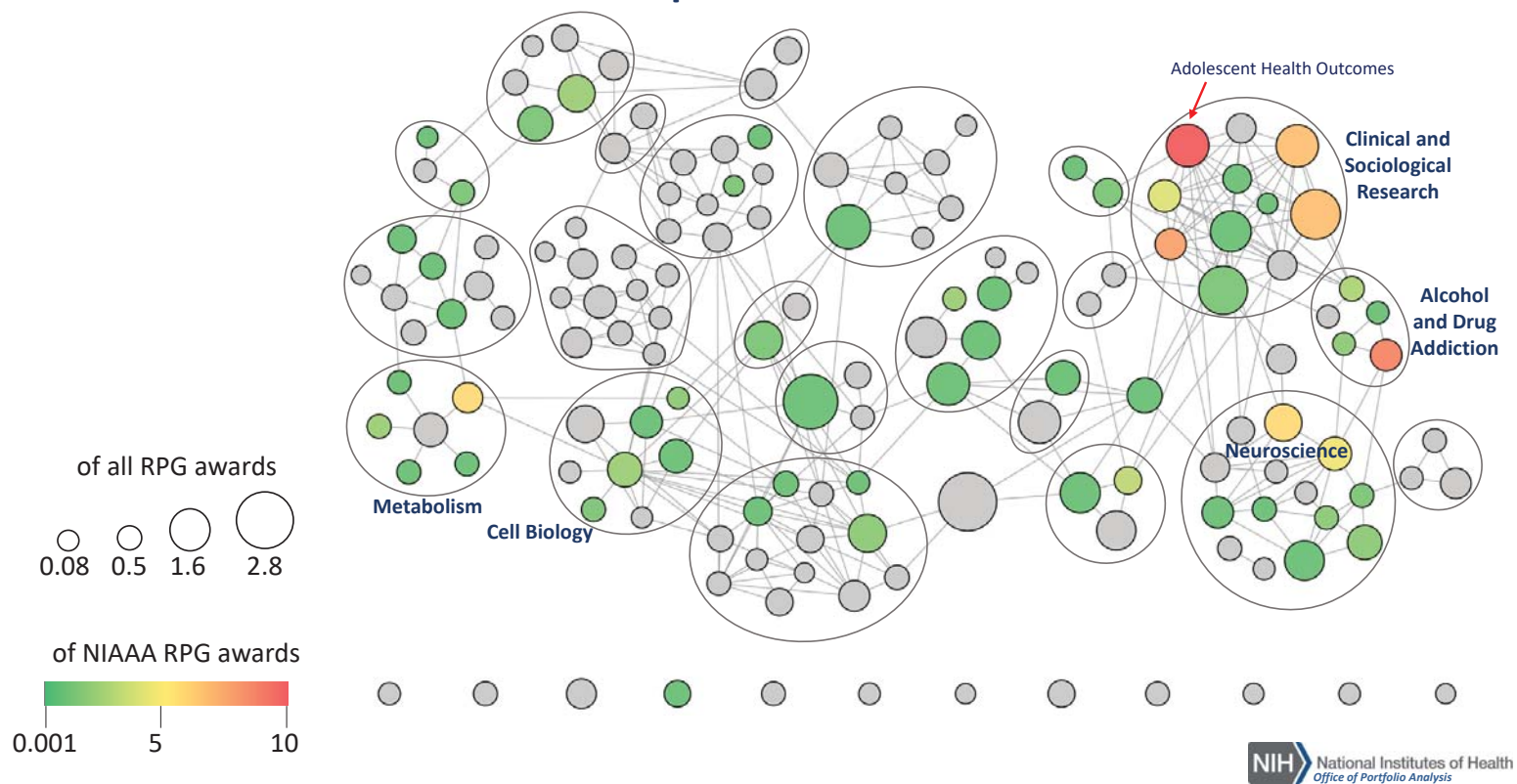
## Word2vec topic clusters of RPG awards (FY2010-FY2017)



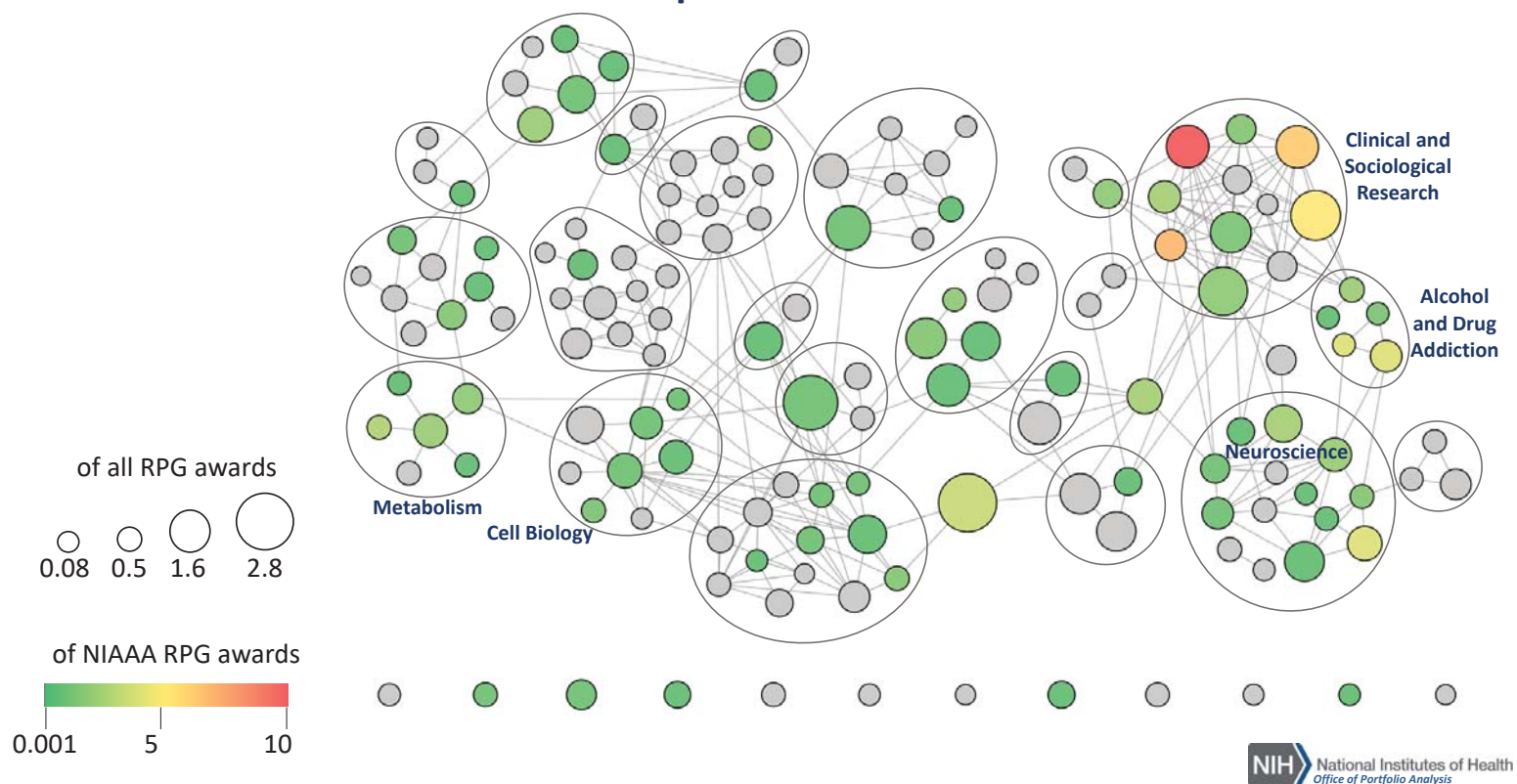
## Word2vec topic clusters of RPG awards (FY2010-FY2017)



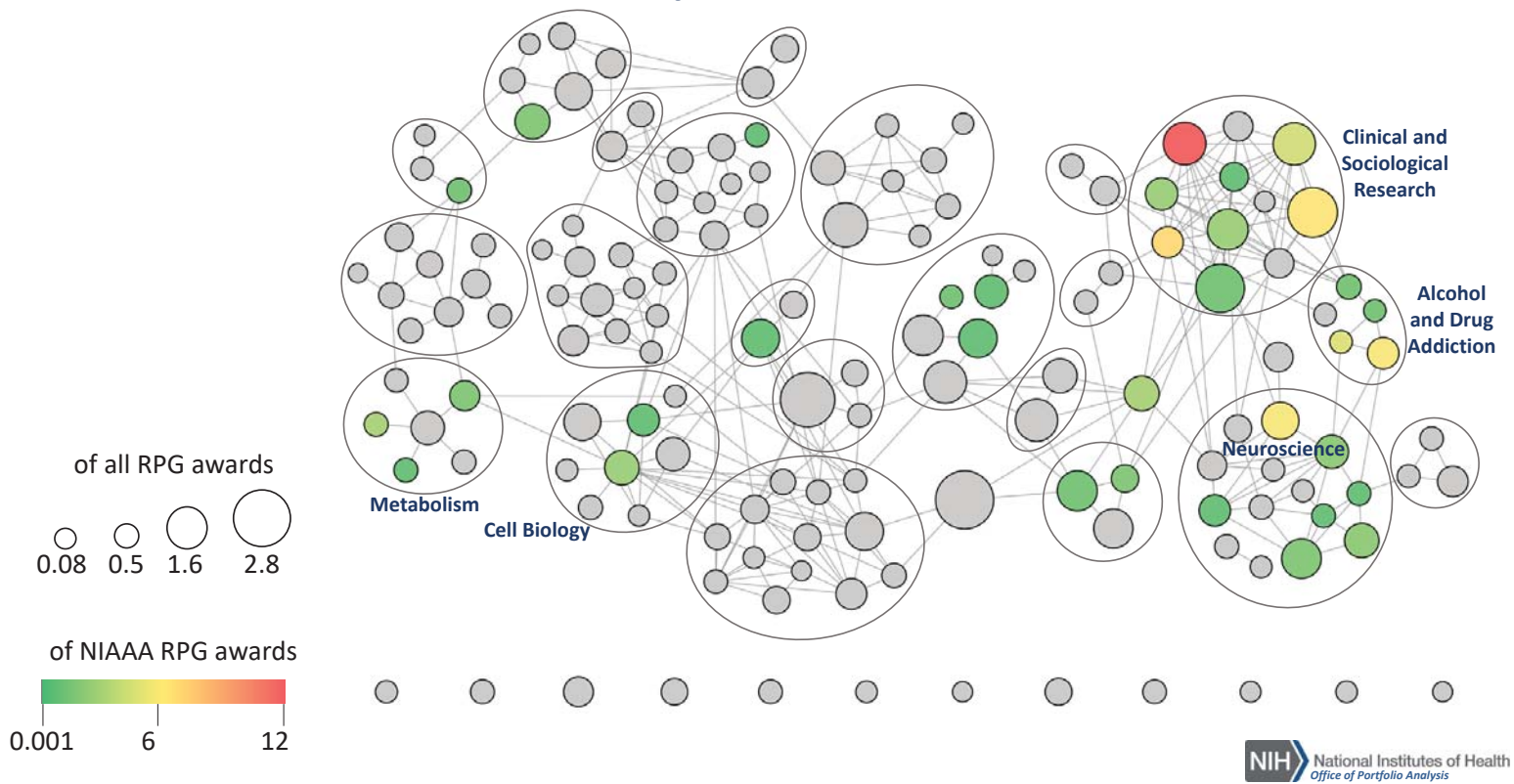
## NIAAA 2008: Topic distribution of awards



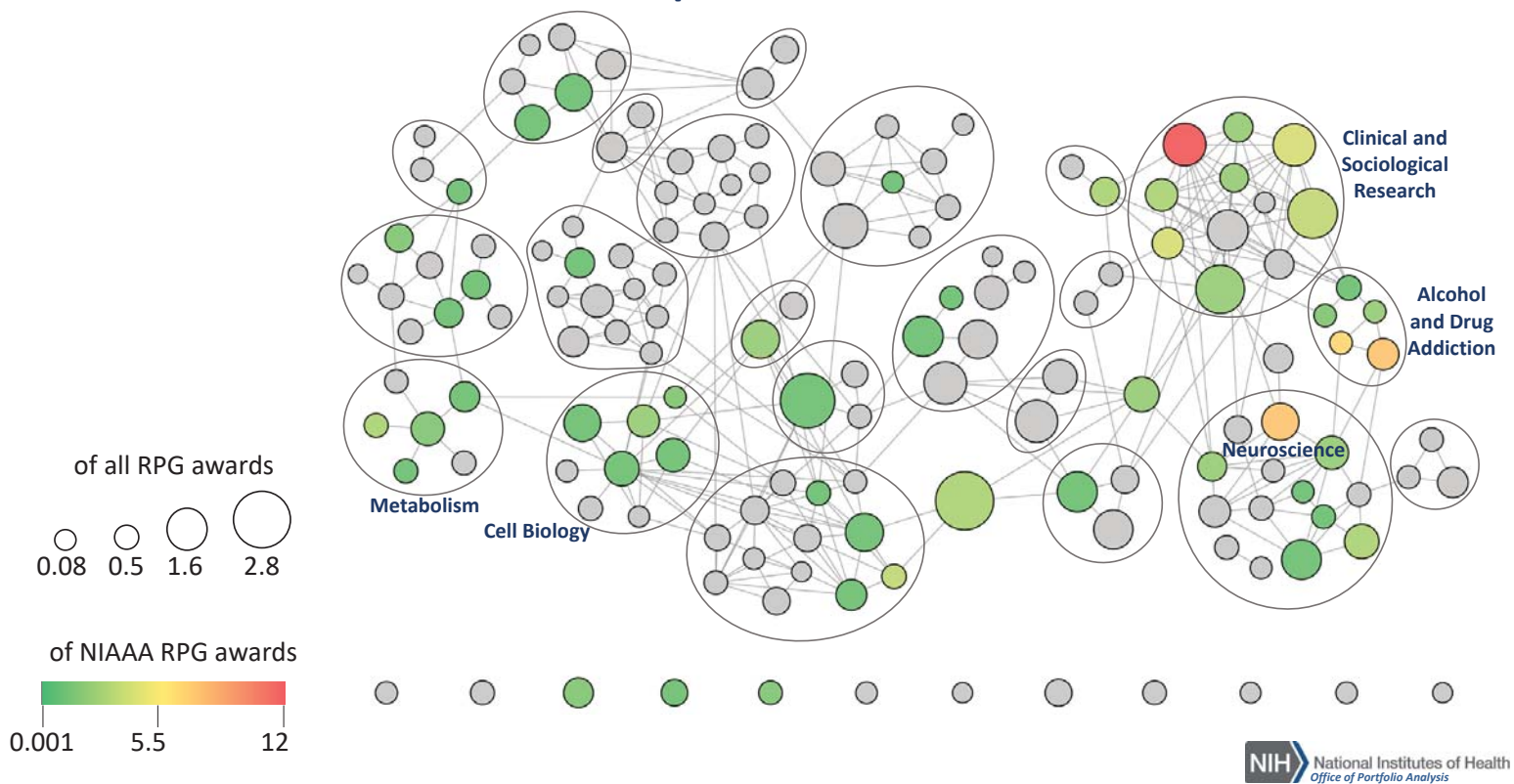
## NIAAA 2009 : Topic distribution of awards



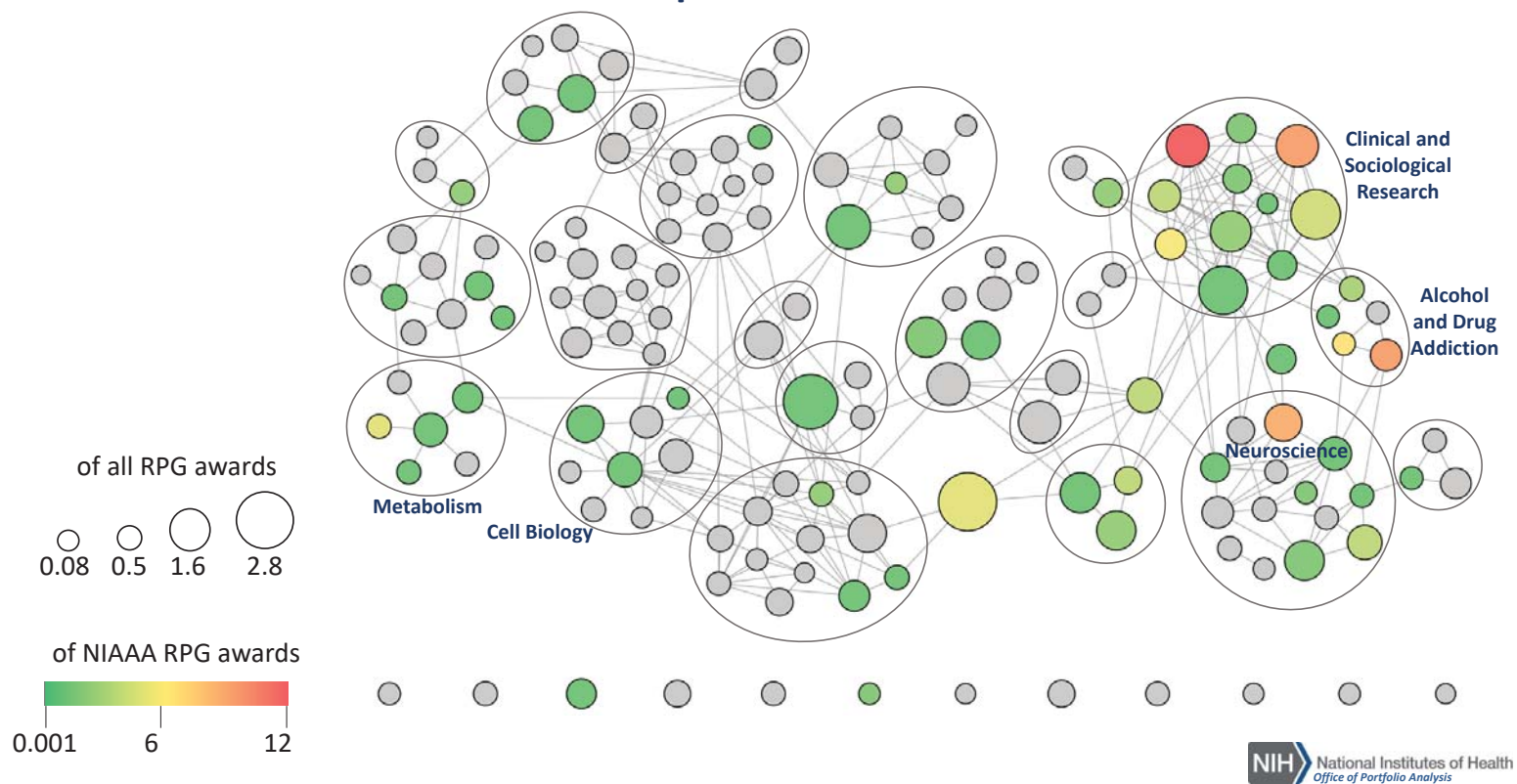
## NIAAA 2010 : Topic distribution of awards



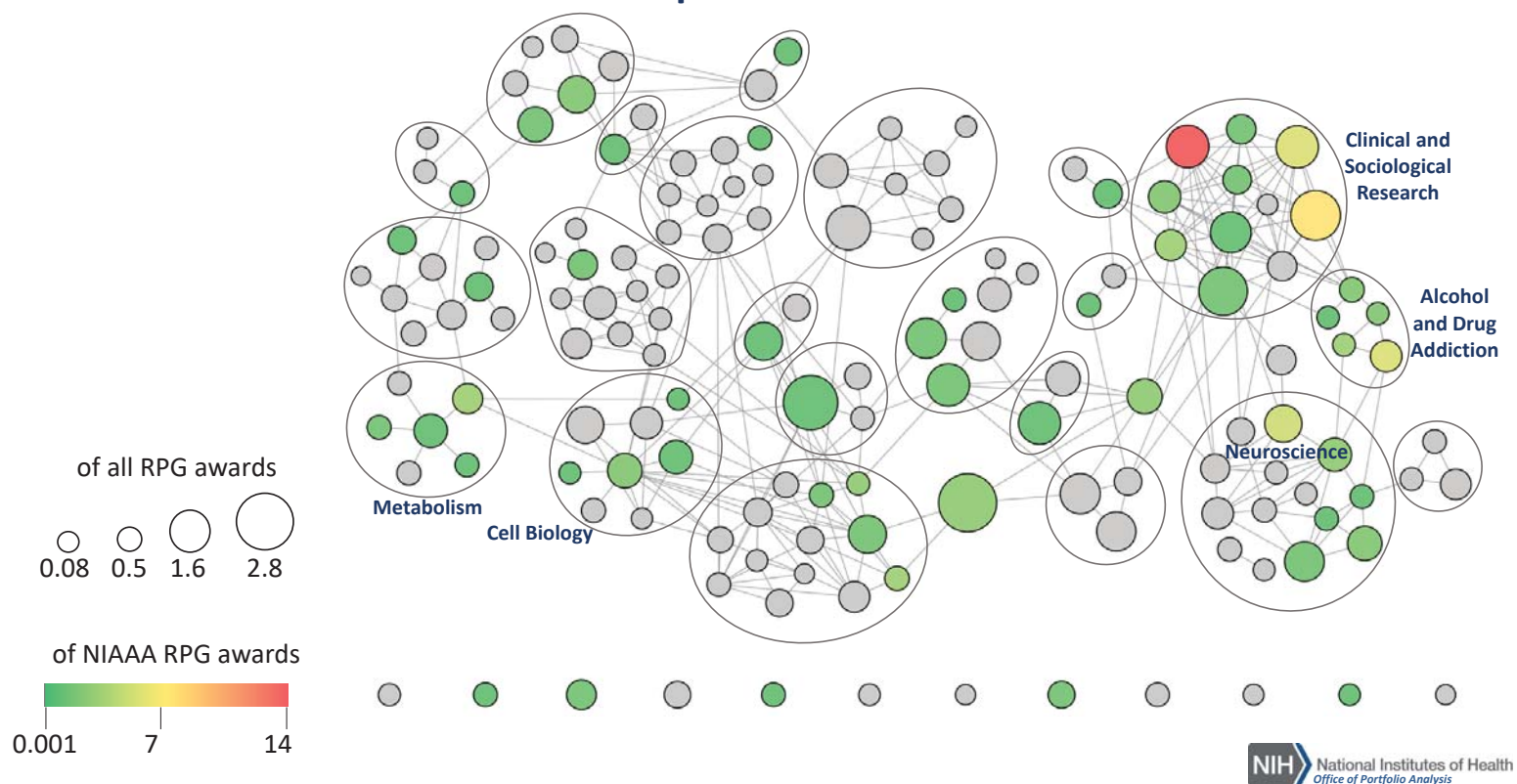
## NIAAA 2011 : Topic distribution of awards



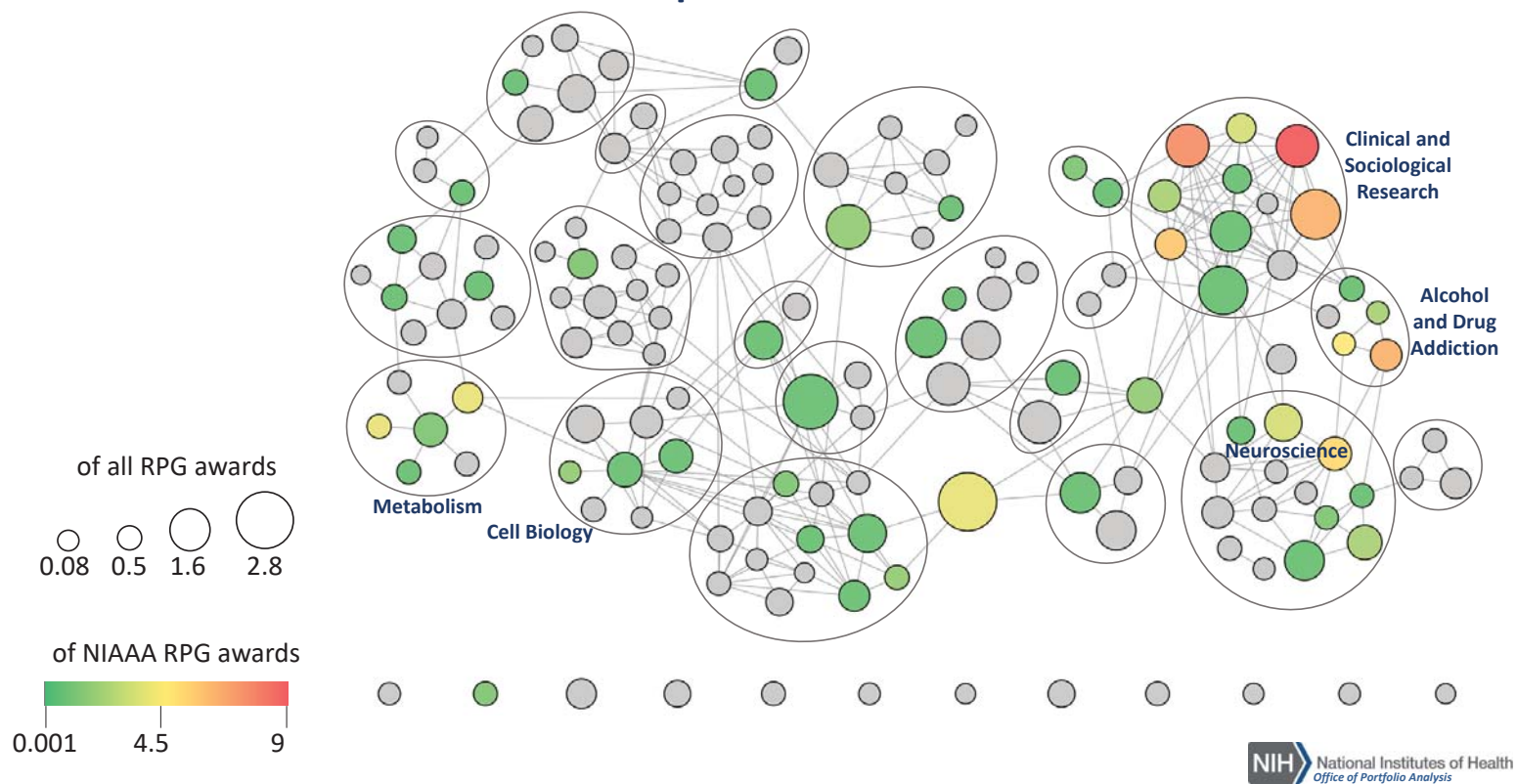
## NIAAA 2012 : Topic distribution of awards



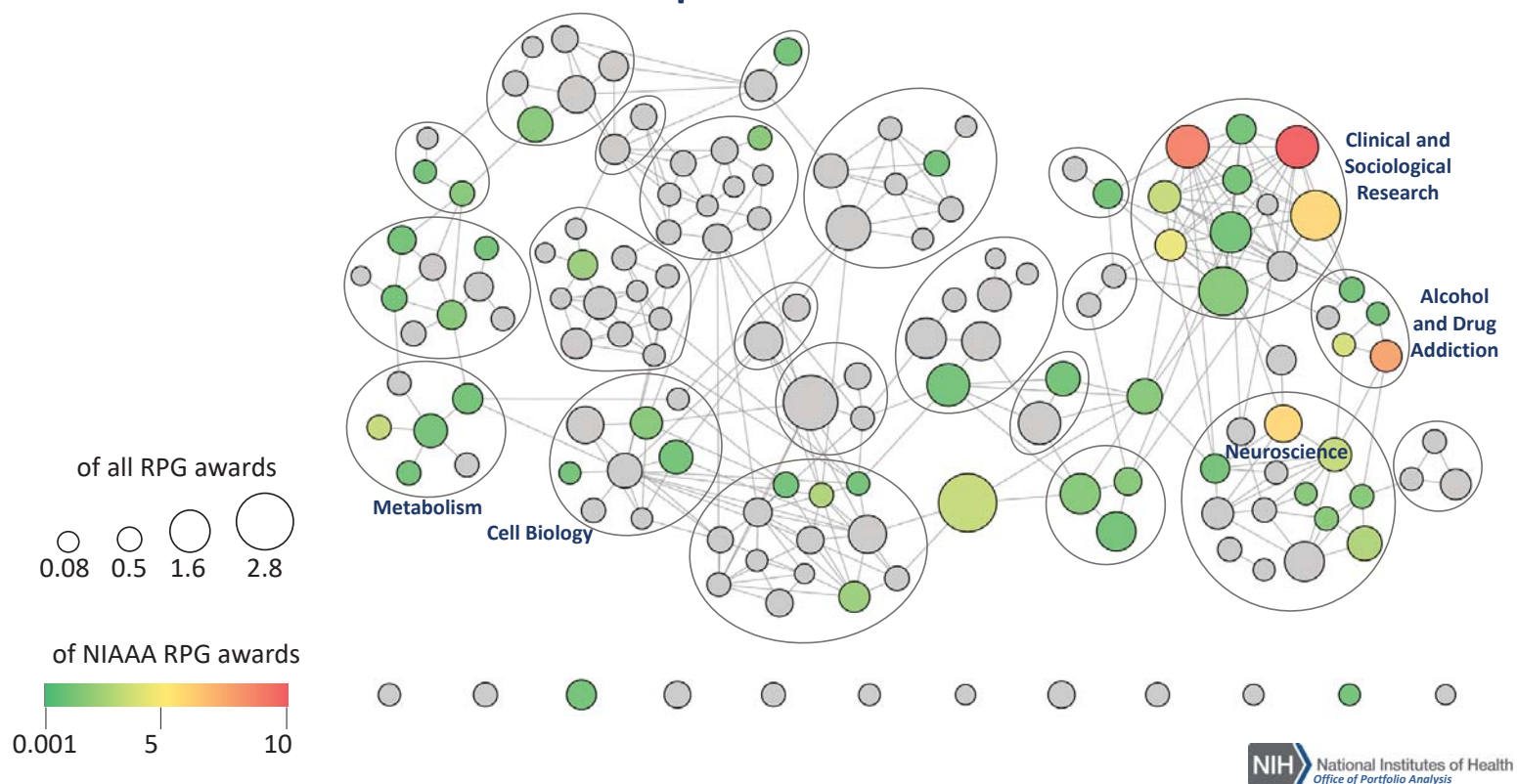
## NIAAA 2013 : Topic distribution of awards



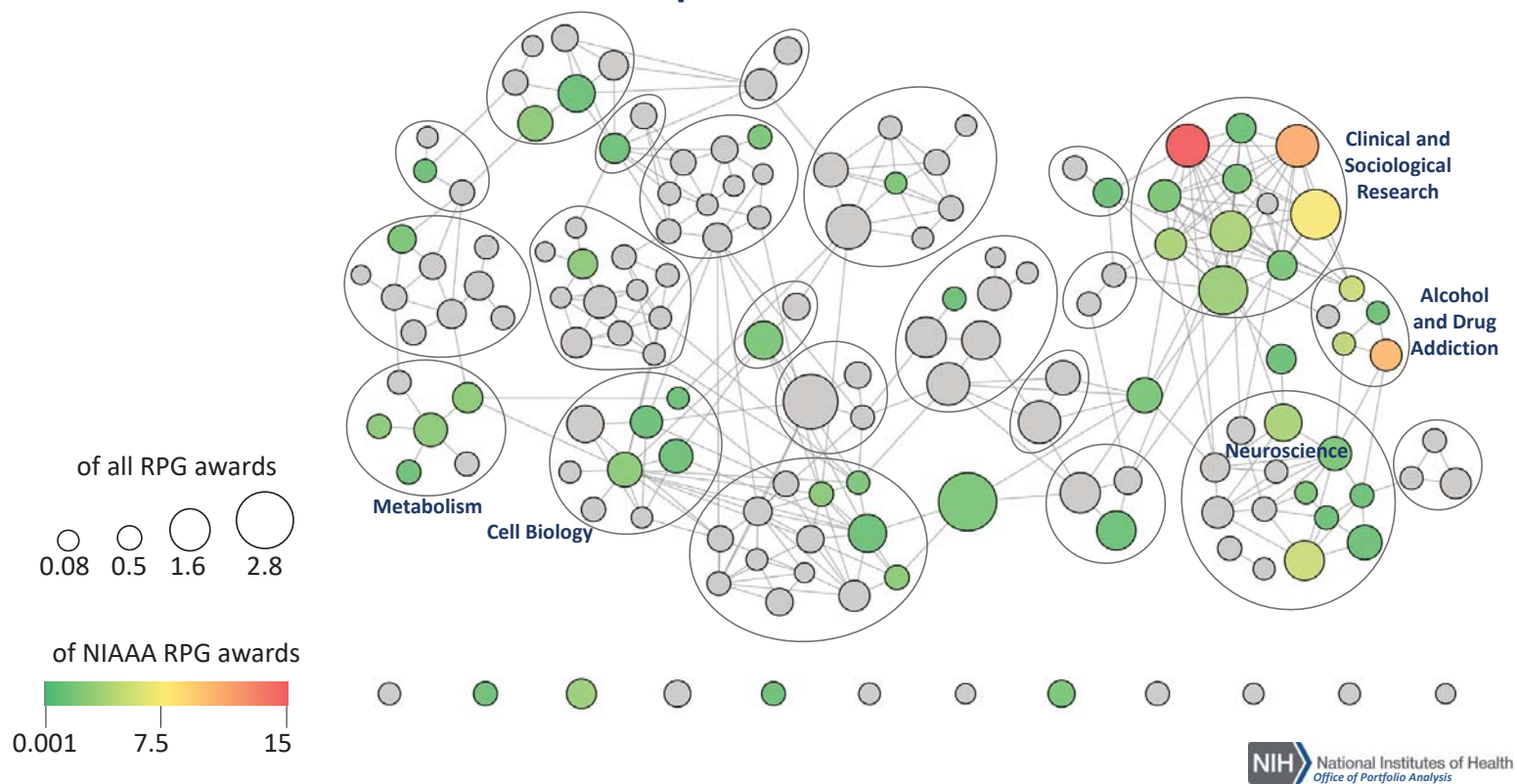
## NIAAA 2014 : Topic distribution of awards



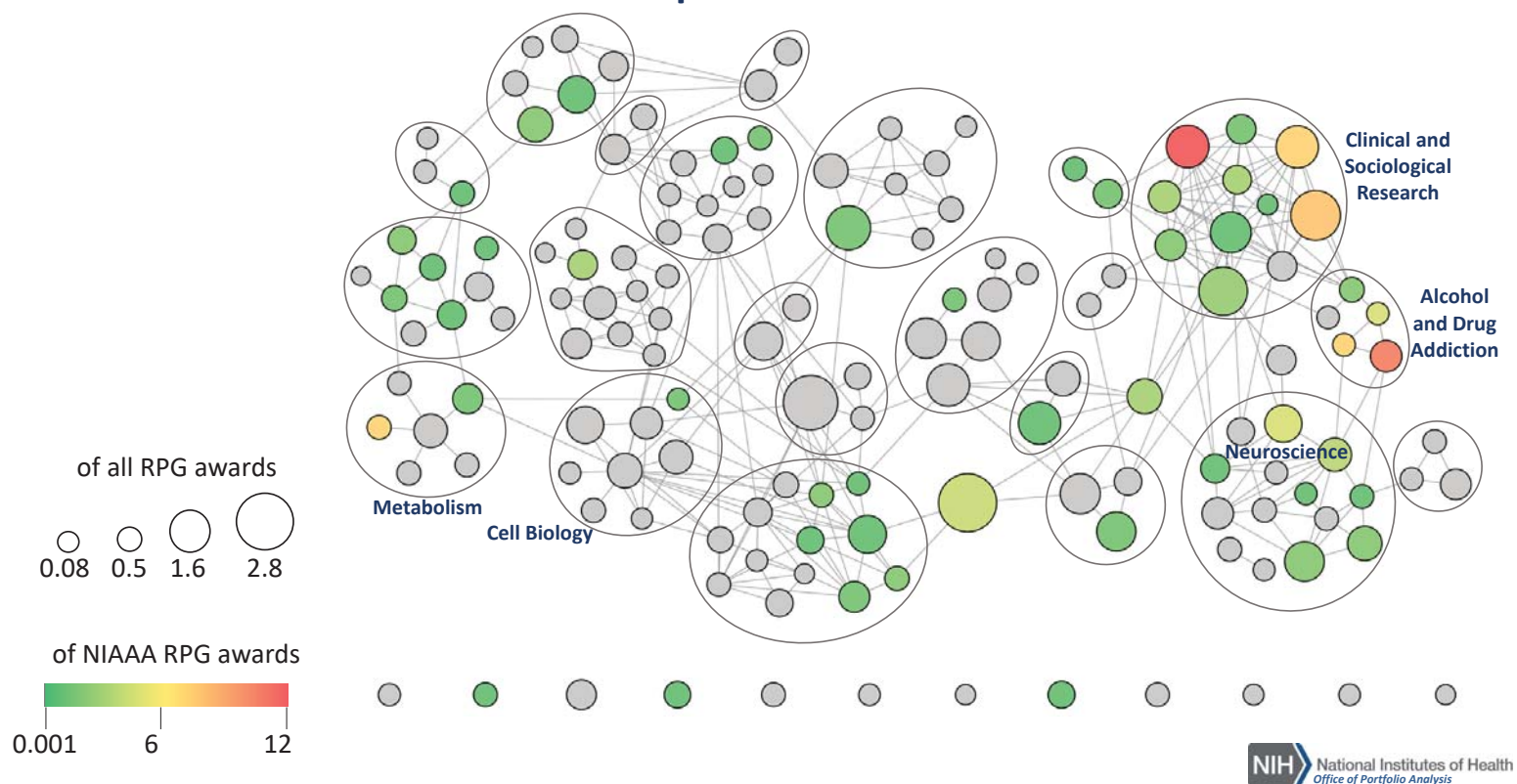
## NIAAA 2015 : Topic distribution of awards



## NIAAA 2016 : Topic distribution of awards



## NIAAA 2017 : Topic distribution of awards



cluster_id	Totals	Node label	#NIAAA_2008	#NIAAA_2009	#NIAAA_2010	#NIAAA_2011	#NIAAA_2012	#NIAAA_2013	#NIAAA_2014	#NIAAA_2015	#NIAAA_2016	#NIAAA_2017
19	200	Adolescent Health Outcomes	20	30	25	16	17	23	13	14	21	21
50	128	Addiction and Cocaine Abuse	17	12	12	10	13	9	11	12	14	18
15	127	Clinical Assessments	13	18	9	6	13	9	16	16	15	12
13	107	Clinical Practices	13	15	13	5	6	12	11	9	10	13
18	93	Sociology of Healthcare	15	20	14	6	8	5	10	7	5	3
42	88	Neuroimaging	11	7	12	10	12	8	6	9	5	8
51	80	Alcoholism	3	12	10	9	9	5	8	6	6	12
143	58	Liver Disease	4	8	6	4	7	2	7	5	3	12
3	50	GWAS Studies	0	10	4	4	7	4	7	5	2	7
41	49	Learning and Cognition	9	6	4	3	1	4	9	5	2	6
11	48	Prevention and Sexual Behavior Intervene	8	7	5	4	5	3	4	5	2	5
34	43	Neuronal Plasticity	3	12	4	4	5	3	4	4	1	3
133	39	Mitochondria and Cellular Respiration	11	5	3	1	1	5	7	1	3	2
4	38	Statistics and Modeling	1	7	6	3	5	4	3	2	2	5
9	33	Smoking Cessation	5	6	2	1	4	3	1	1	7	3
17	26	Health Risk Factors Predictions	2	5	2	3	1	2	1	2	4	4
49	26	Opioid Abuse	1	3	2	3	0	3	4	1	1	8
12	25	Healthcare Delivery	0	4	4	3	2	2	6	1	1	2
119	25	Epigenomic Modification	0	4	1	5	1	5	3	0	3	3
55	23	Innate Immunity	2	6	3	1	1	2	0	2	3	3
14	21	Clinical Outcomes	1	3	5	0	3	1	1	1	5	1
46	21	Neuronal Circuits	1	1	3	1	2	2	1	0	7	3
122	21	microRNA	0	2	3	1	3	2	0	4	3	3
21	20	Childbirth and Infancy	2	5	0	4	3	1	1	1	1	2
125	20	Model Organisms and Genetics	4	2	5	1	1	3	1	0	3	0
146	19	Type 2 Diabetes	0	6	3	2	1	1	2	1	3	0
10	18	Sub-Saharan Africa Epidemiology	1	0	1	3	2	2	1	1	2	5
78	18	Gut Microbiome	0	1	1	1	0	2	2	3	3	5
0	17	Research Resources	6	1	3	0	5	0	0	2	0	0
48	17	G-Protein Coupled Receptors	4	5	2	1	0	1	1	0	1	2
28	14	HIV and Neurodegeneration	1	4	1	0	1	1	0	2	2	2
29	14	Brain Injury and Stroke Recovery	0	2	2	2	1	2	0	1	4	0
33	14	Dopamine Effects	2	4	1	0	1	1	1	2	1	1
103	14	Lung Injury	2	1	2	1	3	1	1	2	0	1
58	13	Th17 Cell Biology	4	2	0	1	1	3	0	0	1	1
91	13	Drug Discovery	0	4	3	1	2	2	1	0	0	0
107	13	Vascular Fibrosis	1	2	0	2	0	1	1	1	2	3
35	12	Epilepsy	3	1	1	1	0	1	2	2	1	0
134	12	Cell Death	3	2	0	0	2	1	1	0	1	2
126	11	Genetics	1	2	0	0	0	4	0	1	2	1
128	11	Stem Cells	2	1	1	3	0	1	1	0	2	0
40	10	Sleep Disorders	0	1	1	1	2	0	0	2	2	1
43	10	Language Processing	0	2	2	3	1	0	0	1	0	1
120	10	Gene Expression Regulation	3	1	0	1	0	2	1	0	1	1
121	10	Histone Modification	0	0	2	1	1	0	1	3	0	2
131	10	Cell Membrane and Vesicular Transport	1	2	1	3	0	0	0	2	1	0
2	9	Biostatistics and Core Services	0	0	2	0	3	0	0	1	1	2
110	9	Oxidative Stress	1	4	0	1	0	0	0	2	0	1
141	9	Tumorigenesis	1	2	0	0	1	0	3	0	0	2
5	8	Software Development	1	0	2	1	1	0	1	2	0	0
27	7	Demyelination Disease	0	2	0	0	1	2	0	0	1	1
36	7	Circadian Rhythms	0	0	2	0	0	1	3	1	0	0
37	7	Appetite Disorders	1	0	1	1	1	0	1	1	1	0
85	7	Protein Crystallography	1	2	0	1	1	1	1	0	0	0
127	7	Morphogenesis	1	1	0	1	0	1	1	1	1	0
142	7	Pancreatic Cancer	0	0	1	1	3	0	0	0	2	0
8	6	Tobacco Use	0	1	1	2	1	1	0	0	0	0
96	6	Osteogenesis	0	1	0	0	0	2	0	0	2	1
87	5	High-throughput Screening	1	1	0	0	0	2	0	1	0	0
101	5	Heart Failure	0	1	0	1	1	1	1	0	0	0
109	5	Vascular Disease	0	0	0	0	1	0	1	1	0	2
118	5	Embryonic Development	2	3	0	0	0	0	0	0	0	0
20	4	Pregnancy and Fetal Development	1	0	0	0	0	0	2	0	0	1
45	4	Information Processing	1	2	1	0	0	0	0	0	0	0
47	4	Sensory and Pain Perception	1	1	0	1	0	0	0	0	0	1
61	4	Gene Therapy	0	0	0	2	0	1	0	0	1	0
89	4	MRI Imaging	1	1	0	0	0	0	1	1	0	0
90	4	Nanoparticle and Drug Delivery	1	1	1	0	1	0	0	0	0	0
123	4	RNA Transcription	0	2	0	0	0	0	1	0	0	1
132	4	Ubiquitination	1	0	0	0	0	2	1	0	0	0
148	4	Metabolism	0	1	1	0	0	1	0	1	0	0
7	3	Diabetes and Cardiovascular Disease	1	0	0	0	1	0	0	0	0	1
16	3	Obesity and Lifestyle Intervention	0	0	0	0	1	0	0	0	2	0
56	3	Transplant Rejection	0	0	1	0	0	1	0	1	0	0
65	3	Vaccination	0	1	0	0	0	1	0	0	1	0
100	3	Heart Arrhythmia	0	1	0	0	0	0	0	1	0	1
145	3	Type 1 Diabetes	1	1	0	0	0	1	0	0	0	0
6	2	Alzheimer's Research	0	0	0	0	1	0	0	0	1	0
38	2	Physical Rehabilitation	0	1	0	0	0	0	1	0	0	0
57	2	T-Cell Immunotherapy	0	1	0	0	0	0	1	0	0	0
88	2	Imaging Methodology	0	0	0	0	0	1	0	0	0	1
93	2	Kidney Diseases	0	0	0	0	2	0	0	0	0	0
97	2	Tissue Scaffolding and Engineering	1	0	1	0	0	0	0	0	0	0
104	2	Lung and Pulmonary Disease	0	0	0	0	0	0	0	1	1	0
108	2	Angiogenesis	1	0	0	0	0	0	0	0	0	1
130	2	Cytoskeleton Dynamics	0	0	0	1	1	0	0	0	0	0
138	2	Breast Cancer	0	0	1	0	0	0	0	1	0	0
139	2	Colon Cancer	0	1	0	0	0	0	1	0	0	0
144	2	Hepatitis C Induced Liver Damage	2	0	0	0	0	0	0	0	0	0
147	2	Cholesterol Management	1	1	0	0	0	0	0	0	0	0
23	1	Environmental Remediation	0	0	0	0	0	1	0	0	0	0
32	1	Huntington and Parkinson's Diseases	0	0	0	0	1	0	0	0	0	0
39	1	Movement Recovery	1	0	0	0	0	0	0	0	0	0
53	1	Asthma and Allergic Response	0	0	0	0	0	0	1	0	0	0
59	1	B-Cell Biology	0	1	0	0	0	0	0	0	0	0
60	1	CD8 T-Cell Biology	0	1	0	0	0	0	0	0	0	0
68	1	HIV Latency	0	0	0	0	0	0	0	0	0	1
92	1	Hypertension	0	0	1	0	0	0	0	0	0	0

cluster_id	Node label	%NIAAA_2008	%NIAAA_2009	%NIAAA_2010	%NIAAA_2011	%NIAAA_2012	%NIAAA_2013	%NIAAA_2014	%NIAAA_2015	%NIAAA_2016	%NIAAA_2017
19	Adolescent Health Outcomes	9.71%	10.24%	12.32%	10.60%	9.60%	13.86%	7.47%	8.86%	12.21%	10.29%
50	Addiction and Cocaine Abuse	8.25%	4.10%	5.91%	6.62%	7.34%	5.42%	6.32%	7.59%	8.14%	8.82%
15	Clinical Assessments	6.31%	6.14%	4.43%	3.97%	7.34%	5.42%	9.20%	10.13%	8.72%	5.88%
13	Clinical Practices	6.31%	5.12%	6.40%	3.31%	3.39%	7.23%	6.32%	5.70%	5.81%	6.37%
18	Sociology of Healthcare	7.28%	6.83%	6.90%	3.97%	4.52%	3.01%	5.75%	4.43%	2.91%	1.47%
42	Neuroimaging	5.34%	2.39%	5.91%	6.62%	6.78%	4.82%	3.45%	5.70%	2.91%	3.92%
51	Alcoholism	1.46%	4.10%	4.93%	5.96%	3.01%	4.60%	3.01%	4.60%	3.80%	3.49%
143	Liver Disease	1.94%	2.73%	2.96%	2.65%	3.95%	1.20%	4.02%	3.16%	1.74%	5.88%
3	GWAS Studies	0.00%	3.41%	1.97%	2.65%	3.95%	2.41%	4.02%	3.16%	1.16%	3.43%
41	Learning and Cognition	4.37%	2.05%	1.97%	1.99%	0.56%	2.41%	5.17%	3.16%	1.16%	2.94%
11	Prevention and Sexual Behavior Intervene	3.88%	2.39%	2.46%	2.65%	2.82%	1.81%	2.30%	3.16%	1.16%	2.45%
34	Neuronal Plasticity	1.46%	4.10%	1.97%	2.65%	2.82%	1.81%	2.30%	2.53%	0.58%	1.47%
133	Mitochondria and Cellular Respiration	5.34%	1.71%	1.48%	0.66%	0.56%	3.01%	4.02%	0.63%	1.74%	0.98%
4	Statistics and Modeling	0.49%	2.39%	2.96%	1.99%	2.82%	2.41%	1.72%	1.27%	1.16%	2.45%
9	Smoking Cessation	2.43%	2.05%	0.99%	0.66%	2.26%	1.81%	0.57%	0.63%	4.07%	1.47%
17	Health Risk Factors Predictions	0.97%	1.71%	0.99%	1.99%	0.56%	1.20%	0.57%	1.27%	2.33%	1.96%
49	Opioid Abuse	0.49%	1.02%	0.99%	1.99%	0.00%	1.81%	2.30%	0.63%	0.58%	3.92%
12	Healthcare Delivery	0.00%	1.37%	1.97%	1.99%	1.13%	1.20%	3.45%	0.63%	0.58%	0.98%
119	Epigenomic Modification	0.00%	1.37%	0.49%	3.31%	0.56%	3.01%	1.72%	0.00%	1.74%	1.47%
55	Innate Immunity	0.97%	2.05%	0.66%	0.66%	0.56%	1.20%	0.00%	1.27%	1.74%	1.47%
14	Clinical Outcomes	0.49%	1.02%	2.46%	0.00%	1.69%	0.60%	0.57%	0.63%	2.91%	0.49%
46	Neuronal Circuits	0.49%	0.34%	1.48%	0.66%	1.13%	1.20%	0.57%	0.60%	4.07%	1.47%
122	microRNA	0.00%	0.68%	1.48%	0.66%	1.69%	1.20%	0.00%	2.53%	1.74%	1.47%
21	Childbirth and Infancy	0.97%	1.71%	0.00%	2.65%	1.69%	0.60%	0.57%	0.63%	0.58%	0.98%
125	Model Organisms and Genetics	1.94%	0.68%	2.46%	0.66%	0.56%	1.81%	0.57%	0.00%	1.74%	0.00%
146	Type 2 Diabetes	0.00%	2.05%	1.48%	1.32%	0.56%	0.60%	1.15%	0.63%	1.74%	0.00%
10	Sub-Saharan Africa Epidemiology	0.49%	0.00%	0.49%	1.99%	1.13%	1.20%	0.57%	0.63%	1.16%	2.45%
78	Gut Microbiome	0.00%	0.34%	0.49%	0.66%	0.00%	1.20%	1.15%	1.90%	1.74%	2.45%
0	Research Resources	2.91%	0.34%	1.48%	0.00%	2.82%	0.00%	0.00%	1.27%	0.00%	0.00%
48	G-Protein Coupled Receptors	1.94%	1.71%	0.99%	0.66%	0.00%	0.60%	0.57%	0.63%</		

99	1	Muscular Atrophy	0	0	0	0	1	0	0	0	0	0
105	1	Cystic Fibrosis	1	0	0	0	0	0	0	0	0	0
111	1	Hematopoietic Stem Cells	0	0	1	0	0	0	0	0	0	0
116	1	DNA Repair	0	1	0	0	0	0	0	0	0	0
124	1	Protein Translation	1	0	0	0	0	0	0	0	0	0
22	0	Pollution and Human Health	0	0	0	0	0	0	0	0	0	0
24	0	Hearing Research	0	0	0	0	0	0	0	0	0	0
25	0	Retinal Degeneration	0	0	0	0	0	0	0	0	0	0
26	0	Glaucoma and Eye Disorders	0	0	0	0	0	0	0	0	0	0
30	0	Neuropathology	0	0	0	0	0	0	0	0	0	0
31	0	Neurodegenerative Diseases	0	0	0	0	0	0	0	0	0	0
44	0	Speech and Hearing Processing	0	0	0	0	0	0	0	0	0	0
54	0	Hypersensitivity	0	0	0	0	0	0	0	0	0	0
62	0	HIV Life Cycle	0	0	0	0	0	0	0	0	0	0
63	0	Viral Replication	0	0	0	0	0	0	0	0	0	0
64	0	Neutralizing Antibodies	0	0	0	0	0	0	0	0	0	0
66	0	RNA Viruses	0	0	0	0	0	0	0	0	0	0
67	0	Influenza Virus	0	0	0	0	0	0	0	0	0	0
69	0	SIV	0	0	0	0	0	0	0	0	0	0
70	0	Herpes Virus	0	0	0	0	0	0	0	0	0	0
71	0	Kaposi's sarcoma-associated herpesvirus	0	0	0	0	0	0	0	0	0	0
72	0	Helicobacter pylori	0	0	0	0	0	0	0	0	0	0
73	0	Lyme Disease	0	0	0	0	0	0	0	0	0	0
74	0	Toxoplasmosis	0	0	0	0	0	0	0	0	0	0
75	0	Malaria	0	0	0	0	0	0	0	0	0	0
76	0	Mosquito-Transmitted Diseases	0	0	0	0	0	0	0	0	0	0
77	0	Chlamydia	0	0	0	0	0	0	0	0	0	0
79	0	Biofilms and Periodontal Disease	0	0	0	0	0	0	0	0	0	0
80	0	Tuberculosis	0	0	0	0	0	0	0	0	0	0
81	0	Fungal Infections	0	0	0	0	0	0	0	0	0	0
82	0	Antibiotic Resistance	0	0	0	0	0	0	0	0	0	0
83	0	Host-Pathogen Interactions	0	0	0	0	0	0	0	0	0	0
84	0	Chemical Synthesis	0	0	0	0	0	0	0	0	0	0
86	0	Protein Glycosylation	0	0	0	0	0	0	0	0	0	0
94	0	Kidney Stone Formation	0	0	0	0	0	0	0	0	0	0
95	0	Tooth Decay	0	0	0	0	0	0	0	0	0	0
98	0	Joint Replacement	0	0	0	0	0	0	0	0	0	0
102	0	Platelet Coagulation	0	0	0	0	0	0	0	0	0	0
106	0	Heart Disease	0	0	0	0	0	0	0	0	0	0
112	0	Anemia	0	0	0	0	0	0	0	0	0	0
113	0	Cell Division	0	0	0	0	0	0	0	0	0	0
114	0	Telomerase	0	0	0	0	0	0	0	0	0	0
115	0	Genomic Instability	0	0	0	0	0	0	0	0	0	0
117	0	DNA Replication	0	0	0	0	0	0	0	0	0	0
129	0	Cilia and Organelles	0	0	0	0	0	0	0	0	0	0
135	0	HPV and Cancer	0	0	0	0	0	0	0	0	0	0
136	0	Skin Cancer	0	0	0	0	0	0	0	0	0	0
137	0	Prostate Cancer	0	0	0	0	0	0	0	0	0	0
140	0	Brain Cancer	0	0	0	0	0	0	0	0	0	0
149	0	Pain Inhibitors	0	0	0	0	0	0	0	0	0	0

1891

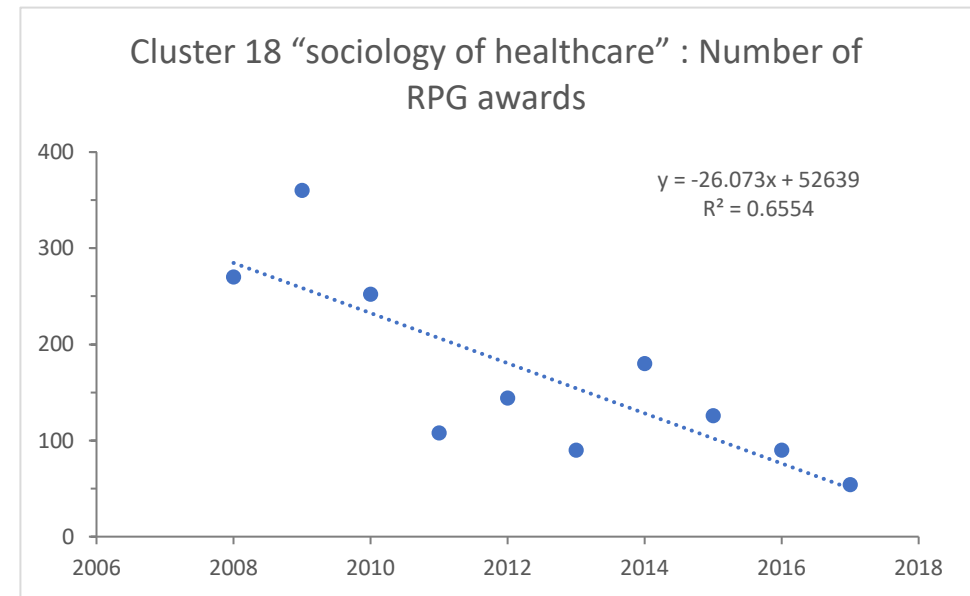
99		Muscular Atrophy	0.00%	0.00%	0.00%	0.00%	0.56%	0.00%	0.00%	0.00%	0.00%	0.00%
105		Cystic Fibrosis	0.49%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
111		Hematopoietic Stem Cells	0.00%	0.00%	0.49%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
116		DNA Repair	0.00%	0.34%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
124		Protein Translation	0.49%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
22		Pollution and Human Health	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
24		Hearing Research	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
25		Retinal Degeneration	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
26		Glaucoma and Eye Disorders	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
30		Neuropathology	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
31		Neurodegenerative Diseases	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
44		Speech and Hearing Processing	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
54		Hypersensitivity	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
62		HIV Life Cycle	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
63		Viral Replication	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
64		Neutralizing Antibodies	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
66		RNA Viruses	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
67		Influenza Virus	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
69		SIV	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
70		Herpes Virus	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
71		Kaposi's sarcoma-associated herpesvirus	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
72		Helicobacter pylori	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
73		Lyme Disease	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
74		Toxoplasmosis	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
75		Malaria	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
76		Mosquito-Transmitted Diseases	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
77		Chlamydia	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
79		Biofilms and Periodontal Disease	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
80		Tuberculosis	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
81		Fungal Infections	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
82		Antibiotic Resistance	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
83		Host-Pathogen Interactions	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
84		Chemical Synthesis	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
86		Protein Glycosylation	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
94		Kidney Stone Formation	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
95		Tooth Decay	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
98		Joint Replacement	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
102		Platelet Coagulation	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
106		Heart Disease	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
112		Anemia	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
113		Cell Division	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
114		Telomerase	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
115		Genomic Instability	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
117		DNA Replication	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
129		Cilia and Organelles	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
135		HPV and Cancer	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
136		Skin Cancer	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
137		Prostate Cancer	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
140		Brain Cancer	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
149		Pain Inhibitors	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%



### Sociology of Healthcare

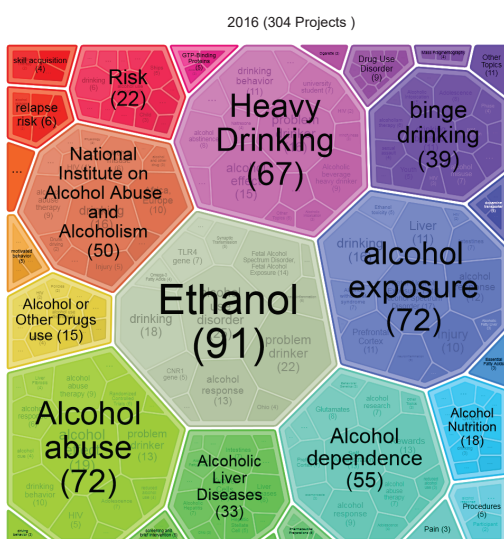
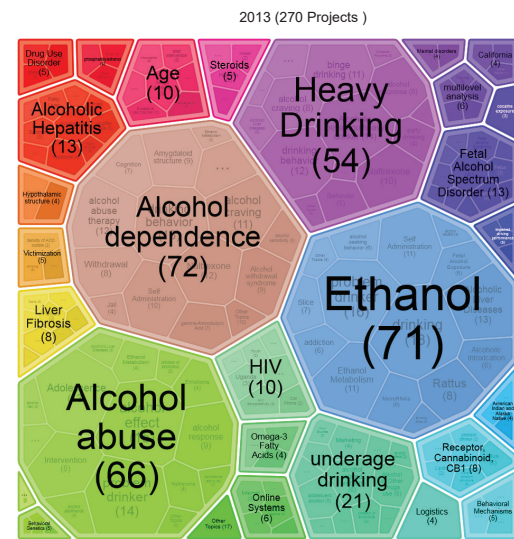
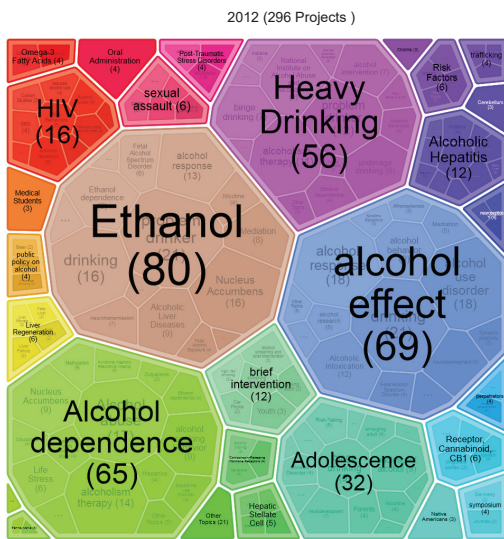
Row Labels	Sum of cluster_id
2008	270
2009	360
2010	252
2011	108
2012	144
2013	90
2014	180
2015	126
2016	90
2017	54
<b>Grand Total</b>	<b>1674</b>

<b>2008</b>	270	16.13%
<b>2009</b>	360	21.51%
<b>2010</b>	252	15.05%
<b>2011</b>	108	6.45%
<b>2012</b>	144	8.60%
<b>2013</b>	90	5.38%
<b>2014</b>	180	10.75%
<b>2015</b>	126	7.53%
<b>2016</b>	90	5.38%
<b>2017</b>	54	3.23%
<b>ALL</b>	<b>1674</b>	<b>100.00%</b>



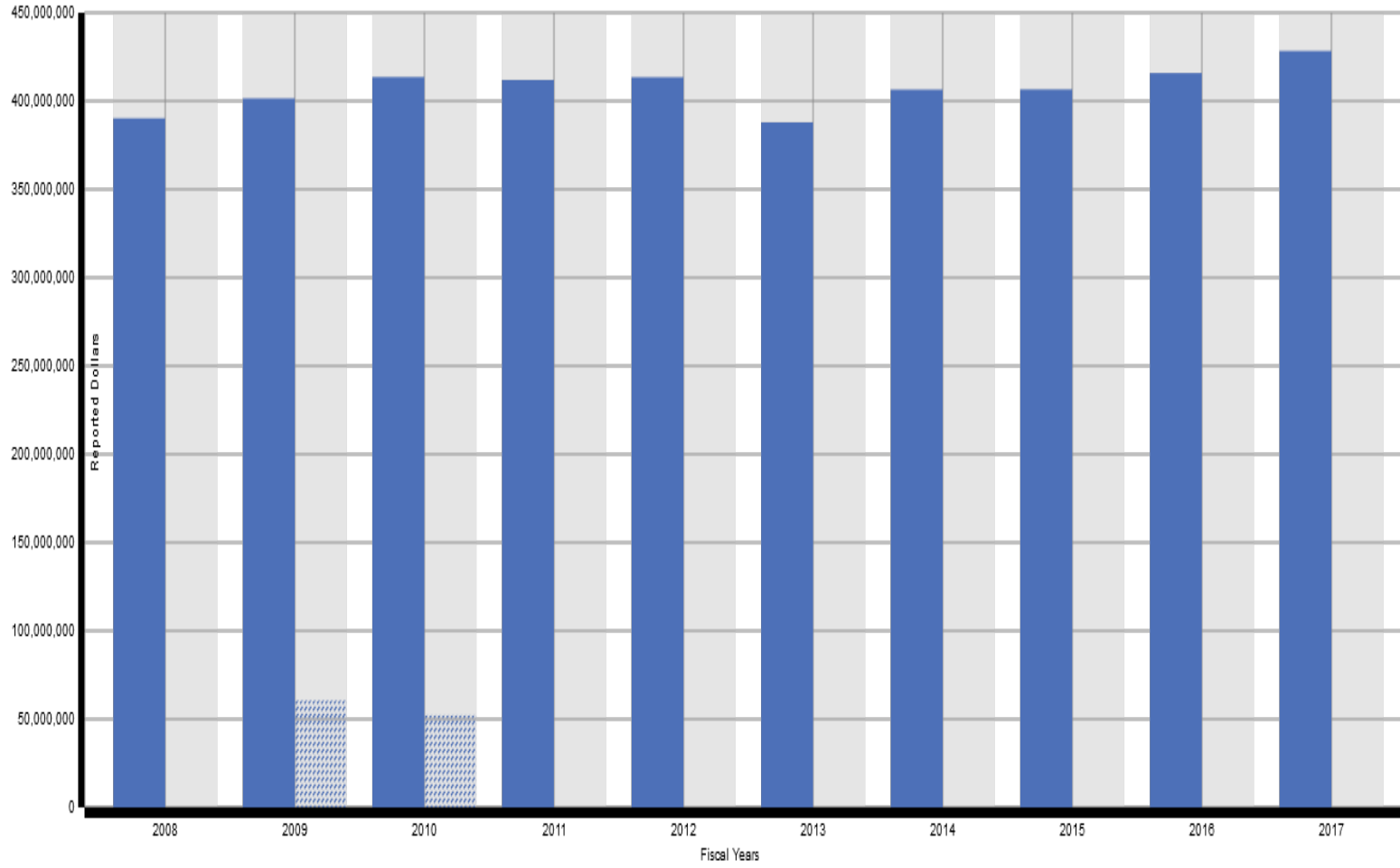
# Appendix Item L.1.(b)

Fiscal Year: 2008, 2009, 2012, 2013, 2016, 2017



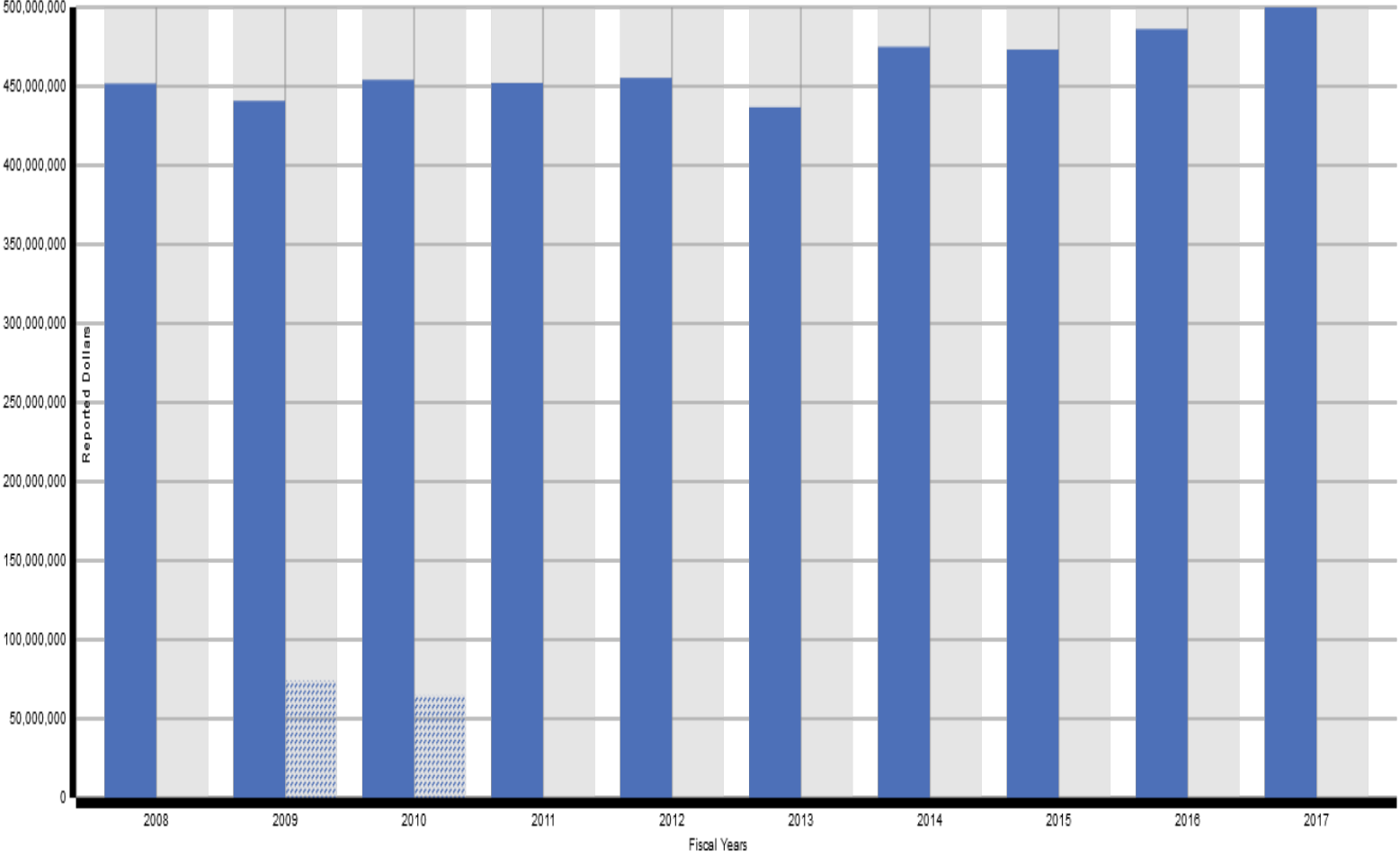
Appendix item L.2.

Multi-Year Category Comparison NIAAA awards only  
From FY 2008 to 2017  
Trend: Reported \$



Base ARRA  
Alcoholism, Alcohol Use and Health

Multi-Year Category Comparison - All NIH Awards  
 From FY 2008 to 2017  
 Trend: Reported \$



Base ARRA  
 Alcoholism, Alcohol Use and Health

### Appendix Item K.3.

## PORTFOLIO ANALYSIS REPORT BY THE OFFICE OF SCIENCE POLICY – ALCOHOL ADVERTISING

### NIAAA-supported research on alcohol advertising

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has supported studies examining aspects of the effects of alcohol advertising on youth and adult drinking for more than 15 years. This analysis examined such studies from 2002-2019<sup>1</sup> using the QVR indexed term “alcohol advertising” (FY2008-2019) or the QVR search term “advertising” (2002-2007) for all funded or pending NIAAA grants. Studies across all populations (adolescent, college, young adult, and adult) are included in this analysis.<sup>2</sup> During the time period examined, the level of support has changed, with the most studies supported between FY08-13, and the fewest studies between FY14-19. Results are summarized in the table below, with additional qualitative analysis following.

Time period	Number of projects receiving funding	Number of new projects funded	Total cost (Direct cost)
FY 2002-2007	5	5	\$3,501,870 (Direct = \$2,642,525)
FY 2008-2013	13	9	\$9,876,283 (Direct = \$7,144,735)
FY 2014-2019	5	0	\$5,614,918 (Direct = \$4,126,970)

In FY2002-2007, most projects on this topic came from unsolicited applications. Four of the new projects from the 2008-2013 timeframe also resulted from unsolicited applications. In FY 2011, a program announcement was issued for “Alcohol marketing and youth drinking” ([PA-11-015](#)). Three of the newly funded projects in FY2008-2013 responded to this PA, which expired May 8, 2014. Other PAs that yielded new projects in this area from 2008-2013 included ones for epidemiology and prevention in alcohol research ([PA-07-448](#); currently active), secondary analysis of existing alcohol epidemiology data ([PA-08-167](#); currently active), science of behavior change ([RM-10-002](#); expired April 2010), and structural interventions for alcohol use and risk of HIV/AIDS ([PA-07-005](#); expired May 2016).

Although no new projects were funded in FY14-19, ongoing support for previously awarded projects continued. Recently, NIAAA has noted that it recognizes the association between alcohol advertising exposure and alcohol consumption by youth and has stated that the IC strategy to move this important area of research forward includes innovative intervention-related studies with the goal of preventing and reducing drinking by youth.

<sup>1</sup> Note that FY19 data are incomplete. Results up to May 18, 2018, were included in the analysis.

<sup>2</sup> The vast majority of studies focused on either adolescent or college-age populations. In the FY 2008-2013 timeframe, one study included all populations over the age of 18, and one study in the FY 2002-2007 timeframe included all adults.