MODERATE DRINKING RCT

BUSINESS CASE

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	[redacted]	*06/11/13*			*First draft*
1.1	[redacted]	*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

Submission Date	*06/11/13*
Requested By	[redacted]
	[redacted]
Project Name	*Moderate Drinking RCT*
Desired Start Date	*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 , 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 though 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 $60 - $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 "AAxxxxxxx-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 glace 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.]