Supporting Statement A for

National Epidemiologic Survey on Alcohol and Related Conditions-III (NIAAA)

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A. Justification

A.1 Circumstances Making Collection of Information Necessary

A.1a Overview

This request is for Office of Management and Budget (OMB) approval for National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III) to be fielded in 2012 by the National Institute on Alcohol Abuse and Alcoholism in conjunction with Westat, through a contract under the data collection authorization of Title 42 USC 285 n (Attachment 1). The NESARC-III will collect information on alcohol use and disorders and related physical and mental disabilities in addition to DNA to be obtained through saliva samples. The planned sample size is 46,500. The target population of the NESARC-III is the civilian noninstitutionalized population, 18 years and older, residing in the contiguous United States (U.S.) and Alaska and Hawaii. The sample will include persons (excluding active duty military) living in households, and selected noninstitutionalized group quarters. This request for OMB approval also includes a pilot test of approximately 100 respondents that will serve the sole purpose of testing the data collection procedures and operations.

There will also be two small methodological subcomponents of the NESARC-III proper that will serve the purposes of providing ongoing validation and assessment of the utility of outcome measures appearing on the major data collection questionnaire, the Alcohol Use Disorder and Associated Disabilities Interview Schedule-V (AUDADIS-V). In the first methodological subcomponent, 1000 respondents participating in the NESARC-III proper will be re-interviewed with a shorter version of the original AUDADIS-V. In the second methodological subcomponent, 700 different respondents participating in the NESARC-III proper will be re-interviewed using a different assessment instrument, the Psychiatric Research Interview for Substance and Mental Disorders (PRISM), covering information on

major outcome variables very similar to those appearing in the AUDADIS-V. NIAAA has conducted such validation/utility tests that have received OMB approval (OMB No. 0930-0151, OMB No. 0925-0455) in the past. The design and procedures associated with each of these methodological subcomponents will be explicated in Sections B.2e and B.2f and discussed within the body of this OMB submission as necessary.

The NESARC-III will be the fourth national survey conducted by NIAAA. The objectives and content areas of the NESARC-III are extremely similar to those of the three prior NIAAA surveys, with the exception of the NESARC-III's provision for collecting saliva samples. Prior NIAAA national surveys included the 1991-1992 National Longitudinal Alcohol Epidemiologic Survey (OMB No. 0930-0151), the 2001-2002 Wave 1 NESARC, and the 2004-2005 Wave 2 NESARC (OMB No. 0925-0484).

A.1b Critical Need for the NESARC-III Data

The gravity of alcohol use disorders and their associated disabilities in the U.S. highlights the need for this proposed data collection activity. Alcohol use disorders are the most prevalent mental disorders in the U.S. and are substantial contributors to mortality, morbidity, and disability. Alcohol use is a factor in more than 10 percent of all deaths and is associated with more than one-half of all traffic fatalities. Alcohol abuse also has been closely linked with cancers of the liver, esophagus, and mouth, and identified as an important risk factor for cardiomyopathy, dysrhythmia, hypertriglyceridemia, depression, coronary heart disease, stroke, suicide, and several adverse fetal effects. According to data from the Wave 1 NESARC, 17.5 million adult Americans (8.5%) were estimated to have alcohol use disorders (i.e., abuse or dependence).

Alcohol use disorders also have enormous consequences not only for the health and welfare of those afflicted with the conditions, but also for their families and children, their employers, and the larger society.

For example, approximately one in four children under 18 years old in the U.S. is exposed to alcohol abuse and dependence in the family. More than one-half of American adults have a family member who has, or has had, alcohol dependence. Of the 11.1 million victims of violent crime each year, almost one in four, or 2.7 million, report that the offender had been drinking prior to the crime. The economic costs of alcohol abuse and alcohol dependence were $184.6 billion for 1998 (the last year for which figures are available), or roughly $638 for every man, woman, and child living in the U.S. Thus, alcohol use disorders impose a staggering, but potentially preventable, burden on our nation.

The NESARC-III represents the operationalization of numerous and critical data needs that must be met to achieve NIAAA's mission of understanding the normal and abnormal biological functions and behavior related to alcohol use, alcohol use disorders, and their social, physical, and mental sequelae, and improving the diagnosis, prevention, and treatment of alcohol use disorders and their associated disabilities. Administrative and legal mandates bearing importantly on the health and safety of our citizens cannot be completely addressed without this data collection activity. The lack of reliable, accurate, and up-to-date prevalence data will have an adverse impact on NIAAA's efforts to reduce widespread illness, disability, and premature death due to alcohol use disorders in the U.S. The NIAAA's ability to respond to its mandate to reduce the burden on society and alleviate the pain and suffering of individuals with these disorders and their family members will be seriously impeded if this information collection activity is not conducted. The NESARC-III will also afford the NIAAA a rare opportunity to achieve a significant increase in its understanding of the underlying genetic and environmental factors that serve to initiate and sustain alcohol use disorders and their associated disabilities. If the collection of this information were not conducted, new scientific knowledge would be lost.

A.2 Purpose and Use of the Information Collection

A.2a Objectives and Purposes/Uses

NESARC-III will serve the purpose of fulfilling a variety of NIAAA data needs from a single source of data. The major objectives and purposes/uses of the NESARC-III are summarized in Attachment 2. The major objectives emphasize the need for Institute Program data on the magnitude of the problem of deleterious alcohol use levels, alcohol use disorders, and their associated disabilities and consequences in the U.S. adult general population. Importantly, prior NIAAA surveys conducted between 1991-1992 and 2001-2002 will provide a valuable baseline against which to gauge trends in the prevalence of alcohol use disorders and their associated disabilities occurring over the past decade. Understanding the distribution of these conditions across important subgroups of the population, especially those defined by age, sex, and race-ethnicity, can also be invaluable in developing rational and scientifically based intervention and prevention programs. NIAAA data needs additionally encompass the requirements for information on treatment utilization and unmet treatment need for these conditions in order to understand the burden on treatment delivery systems and the number and characteristics of individuals in need of treatment for the purpose of planning and re-directing treatment and services to those most in need of them. Data on treatment utilization also will be used by NIAAA to understand the barriers to treatment for alcohol use disorders and their associated disabilities, particularly among low-income groups, women, young adults, and race-ethnic minorities. Program data on disparities in the prevalence of harmful alcohol use and alcohol use disorders, coupled with information on treatment disparities, will both be needed by NIAAA to achieve its objective of eliminating health disparities by identifying and ameliorating the environmental and genetic risk factors that give rise to them.

The NESARC-III was also designed to assess the burden of alcohol use disorders and their associated disabilities using the economic costs of

illness as a framework for expressing in dollar terms their multidimensional impact. Estimates of the various components of economic costs of alcohol use disorders can help direct attention to the most costly alcohol-related disabilities and consequences, thereby assisting scientists, clinicians, and policy makers in their search for strategies to address these problems.

At the heart of the NESARC-III is the objective of identifying environmental and genetic risk factors, and their interactions, that are associated with harmful alcohol use patterns, alcohol use disorders, and their associated disabilities. The sample size of the NESARC-III (N=46,500) defines it as the largest study ever conducted to examine gene-disease associations and gene-environment and gene-gene interactions related to alcohol use disorders and their associated disabilities that are often comorbid. Neither genes nor environment alone can explain why any particular individual develops harmful drinking practices or alcohol use disorders and their associated, often comorbid, disabilities. Rather, risk of these conditions is a complex interplay of multiple genes, multiple environmental factors, and their interactions.

To date, genome-wide association studies (GWAS) have examined about 3 million points of common variation in the human genome. GWAS used genotyping to measure hundreds of thousands of these single base differences such as single nucleotide polymorphisms (SNPs) (that mark variations in genome sequencing), many of which have been shown to be associated with risks of alcohol use disorders and their associated physical and mental disabilities. However, these genomic variants discovered to date can only explain less than 5.0 percent of the genetic risk.

Only recently has it become clear that, in addition to variations in sequence (e.g., SNPs), individuals also have variations in genomic structure. Generally, these variants are known as copy number variations (CNVs), which are variations within the genome that result from deletions or duplications of genomic segments. These can be

quite large, involving millions of bases of DNA. Many scientists believe that CNVs, unlike single base changes studied in GWAS (that have very modest effects on risk), may be more penetrant, that is, have larger effects and be more likely to cause alcohol use disorders and their associated disabilities.

To date, most of the SNP genetic variations have been mapped through the HapMap project. The HapMap project tagged the parts of the whole genome that differed among individuals-the so-called genomic markers- that may be associated with disease. Together with the development of genotyping arrays in which data are used to guide tagging SNP selection, results of the HapMap project were used as the basis for GWAS. In GWAS, cases with and without a disease or condition are compared and significant differences in the frequencies of genetic variants, primarily SNPs, were sought at hundreds of thousands of loci in the genome.

The first generation of GWAS results, as mentioned, has identified genetic variation that fell short of explaining more than a small fraction of genetic risk. Accordingly, research in population genetics has turned toward new mapping projects like the 1000 Genomes Project, the aim of which is to construct a more detailed map of genetic variation in the human genome, going beyond SNPs to CNVs and related variations. Newer genotyping arrays have been and continue to be designed and introduced into the market, significantly improving coverage in addition to being designed for detection of CNV and related variants.

The NESARC-III aims to capitalize on the rapid advances in mapping and genotype arrays to sequence the genome and identify genetic variations (SNPs, CNVs, and related variants) that are associated with harmful drinking patterns, alcohol use disorders, and their associated disabilities. Importantly, the NESARC-III will assess interactions of gene variants with environmental events that also alter gene expression and, ultimately, risk of alcohol use disorders and their associated disabilities. The NESARC-III was also designed to address two major methodological problems of prior gene-disease association studies,

namely, small samples that impeded detection of genetic markers, and lack of reliable and valid phenotypic (outcome) information.

A.2b Information to be Collected

A brief description of the data elements of the NESARC-III is an important preliminary to understanding how NIAAA and other agencies and institutions will use the resulting data. The AUDADIS-V questionnaire contains questions related to: (a) background information, including sociodemographic variables; (b) alcohol use practices, disorders, and alcohol-related social, psychological, and physical consequences; (c) symptoms scales indexing major mood, anxiety, and eating conditions that frequently co-occur with alcohol and drug use disorders; (d) tobacco, medicine and drug use and disorders and related social, psychological, and physical consequences; (e) selected personality traits, including behavior; (f) alcohol, drug, and mental health treatment utilization; and (g) medical conditions related to alcohol consumption.

A major purpose of the NESARC-III is to sequence the entire genome with a view toward elucidating gene-disease associations and studying environmental factors that significantly interact with particular genetic variants. Accordingly, the NESARC-III will collect information on numerous environmental factors previously implicated, either empirically or theoretically, in risk of harmful alcohol use patterns, alcohol use disorders, and their associated disabilities. These include, but are not limited to: (a) physical activity; (b) caregiving roles; (c) discrimination in health care and a variety of other situations arising from race-ethnicity, gender, overweight, sexual orientation, and physical disability; (d) acculturation; (e) perceived stress and social support; (f) adverse childhood experiences; (g) nativity; (h) generational status; (i) sexual orientation; (j) age at first intercourse, condom use, and presence of HIV/AIDS and other sexually transmitted disease; (k) health insurance coverage; (l) executive functioning; (m) disability; and (n) needle sharing.

For the purpose of the NESARC-III, two general types of variables are defined: outcome or dependent variables; and risk factors. Putative environmental and genetic risk factors play a dual role in the NESARC-III survey. In descriptive tabulations of the data, risk factors serve as major classification variables by which outcome variables are displayed. In more substantive analyses, risk factors function as independent or explanatory variables that might additionally be shown to moderate, mediate, or confound the relationship between other risk factors and the major outcomes of interest.

In general, the following variables serve as major outcome measures in the NESARC-III: the prevalence of (a) alcohol and drug use practices; (b) alcohol and drug use disorders; (c) alcohol-related disabilities, including alcohol-related medical and psychological conditions; and (d) treatment status (e.g., treated vs. not treated for an alcohol use disorder).

In the NESARC-III, risk factors are defined as factors that have been theoretically posited or empirically shown to increase the risk of developing heavier drinking levels, alcohol use disorders, and their associated disabilities. Importantly, risk factors collected in the NESARC-III can be broadly classified as environmental (e.g., adverse childhood experiences, acculturation) or genetic (gene frequencies associated with genetic variants). With regard to genetic risk factors, a number of genetic variants (primarily SNPs) have been identified that increase the risk of harmful alcohol use patterns, alcohol use disorders, and their associated disabilities. In addition to these, new genetic variants (CNVs) that incur risks of these disorders and conditions are likely to be discovered in this study as the result of sequencing the entire genome using the most up-to-date maps and sequencing platforms.

A copy of the NESARC-III questionnaire, the AUDADIS-V, along with its associated flashcard booklet, appears in Attachment 3. Attachment 4 contains the PRISM questionnaire that will be used in the

methodological subcomponent of the NESARC-III survey proper to assess the validity and utility of the AUDADIS-V. Since this methodological substudy was designed to assess the utility of AUDADIS-V outcome measures, the PRISM does not include the numerous risk factors appearing on the AUDADIS-V but does share the AUDADIS-V content with respect to outcome measures. In Attachment 5, the objectives and use of questions appearing in the AUDADIS-V and PRISM are described in more detail and in parallel form where appropriate.

A.2c Uses of Information by NIAAA

The NIAAA will use the data collected in the NESARC-III to address its program, policy and research goals as mandated by its mission and described in Sections A.1 and A.2.

A.2d Use of Information by Other Agencies and Organizations

National Institute on Drug Abuse (NIDA). The missions of NIAAA and NIDA are similar, but focus on different psychoactive substances. NIDA has had extensive input into the NESARC-III survey instrument and design and will use the data in much the same way as does NIAAA to achieve its program, policy, and research data needs.

Healthy People 2020 Objectives. Similar to its predecessors, the set of objectives for Healthy People 2020 (currently in draft form) provides benchmarks to track and monitor progress in 10-year health promotion and disease prevention objectives aimed at improving the health of all Americans. Over the past 20 years, NIAAA has contributed substantially to the Healthy People objectives through active participation in the Interagency Workgroup on Healthy People by providing data to track risk factors or determinants of diseases and conditions drawing from its prior nationally representative surveys of

the U.S. population. The Healthy People 2020 objectives that NESARC-III will help to address are broader than those addressed in past NIAAA surveys and include the following:

- Decrease the rate of alcohol-impaired driving
- Decrease the proportion of adults who drank excessively in the previous 30 days
- Reduce average annual alcohol consumption
- Reduce the proportion of persons engaging in binge drinking of alcoholic beverages
- Reduce past-month use of illicit substances
- Increase the proportion of persons who need alcohol and/or illicit drug treatment and receive specialty treatment for abuse or dependence in the past year
- Increase smoking cessation during pregnancy
- Reduce tobacco use by adults
- Reduce initiation of tobacco use by children, adolescents, and young adults
- Eliminate disparities in employment rates between working-aged adults with and without disabilities
- Reduce the proportion of people with disabilities who report on non-fatal unintentional injuries that require medical care
- Reduce the proportion of adults with disabilities who report serious mental health symptoms
- Increase the proportion of people with disabilities who report having access to health and wellness programs
- Increase the proportion of persons with health insurance
- Increase the proportion of adults who are at a healthy weight
- Reduce the proportion of adults who are obese
- Reduce the proportion of older adults who have moderate to severe functional limitations
- Reduce the proportion of adults who engage in no leisure-time physical activity
- Reduce acquired immunodeficiency syndrome (AIDS) among adults and adolescents

- Reduce the number of new AIDS cases among adolescent and adult men who have sex with men
- Reduce the number of new AIDS cases among adolescents and adults who inject drugs
- Increase the proportion of adults and adolescents who have been tested for HIV in the past 12 months
- Reduce nonfatal unintentional injuries
- Reduce nonfatal motor vehicle crash-related injuries
- Reduce the suicide rate
- Increase the proportion of adults with mental conditions-who receive treatment

Sharing of NESARC-III data as an invaluable research resource. Data sharing plans promulgated by the National Institutes of Health dictate dissemination of appropriately de-identified data. Both the NESARC-III genotypic data and a subset of its phenotypic data must be deposited in a NIH-wide database, referred to as dbGaP, for the purpose of data sharing. In addition, limited use datasets will be available to researchers interested in this extremely rich research resource base through the NIAAA Data Access Committee. As an important aside, prior NIAAA surveys have been among the most widely used datasets in the history of the NIH. For example, NIH researchers and investigators from a variety of other institutions and agencies have produced over 400 high-quality articles using data from Waves 1 and 2 of the NESARC. This extent of use of data from a federally sponsored survey is unprecedented. It is anticipated that the extent of high-quality investigations using the NESARC-III data will exceed that of prior surveys, especially given the additional provision for DNA collection.

A.3 Use of Information Technology and Burden Reduction

Westat uses appropriate technology to keep respondent burden to a minimum. Examples of information technology approaches to be used to minimize burden during NESARC-III study interviews include:

1. Use of a CAPI household screener prior to the AUDADIS-V administration to determine household eligibility and to select a sample person for the NESARC-III;

2. Use of lead-in questions and logic-based question routing to skip entire sections or questions that are not relevant to a sample person;

3. Use of flashcards to aid sample persons with multiple response categories;

4. Proper arrangement of sections and questions in the AUDADIS-V interviews that will make sense to the sample person and will facilitate the flow of administration from one topic area to another;

5. Use of data collectors who are bilingual in English and Spanish, and English and one of four Asian languages (Mandarin, Cantonese, Korean and Vietnamese); and

6. Use of Spanish versions of all instruments, consent forms and other survey documents for households where Spanish is the only language spoken or is the respondent's or sample person's preferred language for the interview, as well as instruments in the four Asian languages identified above.

All of the NESARC-III questionnaires are computer-assisted (CAI) and all survey responses will be recorded into the CAPI instruments. The questionnaire is designed in separate modules and in all but a few sections there are lead-in questions that are asked to check for relevance in order to quickly skip out of the non-relevant modules. This design was successfully used in both Waves 1 and 2 of the NESARC. Based on the experiences from those implementations, the average sample person was asked questions in about one-third of the total number of sections. Further, within each section, generally only one-third of the associated questions are applicable to any particular respondent, leaving two-thirds inapplicable and therefore unasked. NESARC-III is similarly designed and it is expected to have an equivalent experience.

A Privacy Impact Assessment (PIA) for the NESARC-III Study Management System (N3SMS) was promoted on December 2, 2010 (see Attachment 6).

A.4 Efforts to Identify Duplication and Use of Similar Information

During the development of the proposed data collection activity, numerous individuals were consulted both formally and informally. Consultation included not only issues of study design, sampling design and questionnaire content, but also knowledge of existing surveys or data. In addition, a search was made of the research literature on alcohol use and disorders and associated physical and mental disabilities, and existing documentation was reviewed. Websites of all NIH institutes and offices, as well as all other federal agencies that collect data on alcohol use, alcohol use disorders, and their associated physical and mental disabilities, were searched.

The outcome of this extensive review indicated no past, current, or planned survey duplication of the NESARC-III with respect to its: (a) nationally representative sampling design; (b) sample size; (c) scope and coverage of drinking practices and alcohol-related consequences; (d) coverage of environmental risk factors strongly associated with drinking practices and patterns, alcohol use disorders, and their associated physical and mental disabilities; (e) inclusion of measures based on the Diagnostic and Statistical Manual of Mental Disorders - Fifth Revision (DSM-V: American Psychiatric Association); (f) suitability of income-related variables for econometric purposes; and (g) provision for additionally collecting DNA. No past, current, or planned national data collection has achieved or will achieve the precision of the NESARC-III data with regard to estimates of the prevalences of major outcome measures and risk factors.

In summary, the outcome of this extensive review indicated that there exists no similar information already available, or the collection of

which is currently anticipated, that can be used or modified to address the objectives and uses of the NESARC-III data as described in Sections A.1 and A.2 of this OMB submission. There are numerous other reasons why the NESARC-III data are unique:

1. The NESARC-III sample (N=46,500) provides the most reliable national estimates of the prevalence of harmful alcohol use, alcohol use disorders, and their associated disabilities to date. No other national study on alcohol use disorders and their associated disabilities conducted in the U.S. has included samples of this size, thereby precluding reliable prevalence estimates. Moreover, the NESARC-III is a probability sample of the U.S. population large enough to provide estimates that can be displayed by a number of sociodemographic characteristics. In addition to its size, the NESARC-III includes oversampling of Blacks, Hispanics or Latinos, and Asians, ensuring adequate numbers of major race-ethnic subpopulations suitable for many reliable statistical analyses. No comparable data exist in this country.

2. The NESARC-III is also unique in its approach to quantifying alcohol consumption. Very few studies on alcohol use and alcohol problems conducted since the early 1960s have collected suitable data on alcohol intake. The NESARC-III not only provides for reliable and valid measures of beverage-specific quantity and frequency of ethanol consumption, but also includes indices of duration of use and variation in drinking styles and patterns such as steady daily drinking, regular heavy drinking, binge drinking, and episodic drinking. This multidimensional representation of alcohol consumption, in combination with diagnoses of alcohol use disorders, will enable NIAAA to address urgent issues regarding the risks of developing these disorders at various levels of ethanol intake and for different durations and patterns of use.

3. The NESARC-III alcohol consumption measures are complemented with a series of life-size beverage glasses representing drink sizes in order to help respondents estimate their ethanol intake more accurately. To our knowledge, no general population surveys other than those conducted by NIAAA on alcohol have ever used this technique. Further, extensive beverage container-ethanol equivalency conversion tables developed by NIAAA over the past 2 decades will be used during the data processing stage

of the survey to ensure an accurate representation of respondents' ethanol intake.

4. NIAAA surveys are unique among all federally sponsored surveys in their stringent assessments of the psychometric properties of major survey variables, including test-retest reliability, utility and other methodological studies. These tests, conducted over the last 13 years, have documented that the AUDADIS-V questionnaire is the most reliable and valid assessment instrument of its kind, particularly among general population samples in which it was designed to be used (Drug and Alcohol Dependence, entire volume 47, 1997; Drug and Alcohol Dependence, 44:133-141, 1997; European Addiction Research, 40:89-97, 1997; Drug and Alcohol Dependence, 39:37-44, 1995; Drug and Alcohol Dependence, 71:7-16, 2003; Drug and Alcohol Dependence, 92:27-36, 2008; Journal of Studies on Alcohol, 60:790-799, 1999; also see Molecular Psychiatry, 14:1051-1066, 2009, for summary).

Assessment of the psychometric as well as other properties of AUDADIS-V outcome measures has been an ongoing process for NIAAA survey instruments over the past two decades. The NESARC-III Reliability and Validity Study methodological survey components represent the latest contribution to these data quality approaches.

A.5 Impact on Small Businesses or Other Small Entities

No small businesses or other small entities will be involved in the NESARC-III.

A.6 Consequences of Collecting the Information Less Frequently

If the NESARC-III is not conducted, or is conducted less frequently (more than 7 years between each successive survey), it will not be possible for NIAAA to achieve fully its mandated program and policy objectives of discovering causes of alcohol use disorders and their associated disabilities and developing prevention measures and

treatments for these public health problems which each year cost this country tens of thousands of lives, billions of dollars, and immeasurable suffering and pain. Not conducting the NESARC-III or delaying its implementation will significantly reduce NIAAA's ability to capitalize on major advances in science (e.g., the completion of the Human Genome Project and HapMap, rapid developments in statistical genetic association studies) that have paved the way toward fuller understanding of genetic variation and its associations with disease, as well as the interactions of genetic variants with environmental factors that eventuate in causality.

A.7 Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This project fully complies with the guidelines of 5 CFR 1320.5.

A.8 Comments in Response to the Federal Register Notice and Efforts to Consult Outside Agency

A.8a Federal Register Notice

A copy of the 60-day Federal Register Notice, required by 5 CFR 1320.8 (d), soliciting comments on the information collection prior to submission to the OMB, was published on October 15, 2010 in the Federal Register (Vol. 75, No. 199/p. 63490-91). There were no comments on the collection of information elicited from the 60-day Federal Register Notice. The 30-day Federal Register Notice was submitted for publication to the NIH Office of Management Assessment on December 15, 2010.

A.8b Efforts to Consult Outside Agency

Individuals from within NIH and DHHS and numerous outside agencies and institutions were consulted from July, 2007 to the present, and these consultations are ongoing. The individuals consulted include, but are not limited to, NIAAA's NESARC-III Genetic Advisory Committee established to provide ongoing recommendations and consultation on the genetic component of the NESARC-III data collection activity. They provided significant input on sampling design and methodology, data uses, genetic statistical methods, DNA repository requirements, and data sharing plans. The names, affiliations, and phone numbers of these committee members appear in Attachment 7.

Numerous other individuals who have contributed their expertise regarding sample design and methodology, questionnaire content, and related survey issues also are identified in Attachment 7. Westat staff who most significantly contributed to the design of this study also have been listed, since they are considered experts in their respective fields both within and outside the federal government. Much of the valuable contribution of individuals consulted within and without the NIH was solicited widely by the NIAAA through email notifications. There were no issues raised during the aforementioned consultations.

A.9 Explanation of Any Payment or Gift to Respondents

Many in-person household-based surveys have experienced decreasing response rates in recent years. Table 1 illustrates declining response rates for several major in-person household-based surveys with respondents age 12 years and older:

Table 1. Response Rates for In-person Household-Based Surveys

National Health Interview Survey (NHIS) Adult Questionnaire (1 adult per household)	Medical Expenditure Panel Survey (MEPS) Round 1 (1 adult answering all questions for household)	National Crime Victimization Survey (NCVS) (persons 12+ in household)	National Survey on Drug Use and Health (NSDUH) (1-2 persons 12+ per household)
80.0% (1997)	80.6% (2001)	84.8% (1997)	71.3% (2002)
67.8% (2007)	76.0% (2007)	78.3% (2007)	66.1% (2007)

Response rates are unweighted.

As one part of the planned efforts to meet NESARC-III response rate goals, two levels of incentives are proposed: one for the screener and one for the AUDADIS-V. A modest $10 incentive will be provided to the screener respondent at the completion of the screener interview. This payment should serve to establish a social contract with the household and increase the likelihood of the sample person agreeing to and completing the AUDADIS-V.

In addition to the $10 screener incentive, NIAAA proposes to provide a payment of $90 to the sample person for the AUDADIS-V interview. In a significant number of cases, the screener respondent will be the sample person, and will therefore receive the full $100 incentive. The AUDADIS-V interview, similar to the content and length of its predecessors used in the Waves 1 and 2 NESARC, takes approximately 45-60 minutes to complete on average. The $90 incentive payment is solely tied to participation in the AUDADIS-V interview. The incentive payment is not associated with the sample person’s decision to provide a saliva sample and the sample person receives no additional financial incentive for providing the DNA.

The AUDADIS-V $90 incentive will be provided in two parts: 1) prior to beginning the AUDADIS-V interview, sample persons will be provided with a $45 check; and 2) immediately following the completion of the

AUDADIS-V interview, sample persons will be provided with the remaining $45 check. NIAAA proposes that the incentive payment be split in this manner to increase the likelihood that sample persons will agree to begin and complete the AUDADIS-V. Providing half of the incentive at the beginning of the interview will motivate sample persons to participate in the study. Additionally, the motivation of the remainder of the payment should increase the likelihood that they complete the full AUDADIS-V interview.

The incentive payments will be mentioned in the advance letter sent to each selected household prior to contact by the data collector. It will be clear in the materials that the screener will identify whether any household member is eligible to be selected for the AUDADIS-V interview. The $10 incentive will be provided to the household member completing the screener. Then if a sample person is selected, the $90 incentive will be provided for the AUDADIS-V interview. The advance letter is reviewed prior to the screener, as well as the AUDADIS-V, if the sample person differs from the respondent providing the screening information. Additionally, an explanation of the incentive will be included in the consent document provided to each SP prior to the start of the AUDADIS-V interview.

Interviewers will be required to confirm that the payments were received by the respondents by entering a “1” (for yes) on the relevant computer screen. This procedure is used to ensure that there is no hard copy or computerized record of the name of the respondent. (**See Attachment 8 for a diagram of the flow of the NESARC-III interview as well as the consent documents and procedures, advance letter, and DNA collection procedures and associated scripts and screenshots.**)

OMB approved a similar $80 2-part incentive for the NESARC study conducted in 2004-2005. Justification for providing these incentive payments in two parts lies foremost in the response rate results of 86.7%. (See Attachment 9 that contains an analysis of results of the 2004-2005 NESARC incentive scheme.) NIAAA is proposing a modest

$10 increase to $90 for the NESARC-III AUDADIS-V interview, to adjust for inflation between 2004 and 2012 (based on an approximate annual inflation rate of 1.5 percent per year).

A.10 Assurances of Confidentiality Provided to Respondents

A.10a Overview

Concern for privacy plays a central role in the implementation of the NESARC-III. Such protection is provided to respondents and sample persons under the authority of 42 U.S.C. 241(d). It reads as follows:

> "[t]he Secretary [of Health and Human Services] may authorize persons engaged in research on mental health, including research on the use and effect of alcohol and other psychoactive drugs, to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

The authority of 42 U.S.C. 241(d) has been delegated by the Secretary of Health and Human Services to the National Institutes of Health of which NIAAA is a part. Any person engaged in the research to which this part applies, who desired authorization to withhold names and other identifying characteristics of individuals who are subject to such research from any person or authority not connected with the conduct of such research may apply to the Office of the Director, National Institute on Alcohol Abuse and Alcoholism for an authorization of confidentiality (also called a Certificate of Confidentiality). Persons authorized by the NIH to protect the privacy of research subjects may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify them by name or other identifying characteristic.

A Certificate of Confidentiality protects personally identifiable information about subjects in the research project while the Certificate is in effect. Generally, Certificates are effective on the date of issuance or upon commencement of the research project if the latter occurs after the date of issuance. The expiration date should correspond to the completion of the study. The Certificate will state the date upon which it becomes effective and the date upon which it expires. A Certificate of Confidentiality protects all information identifiable to any individual who participates as a research subject during any time the Certificate is in effect. The Protection afforded by the Certificate is permanent. A Certificate of Confidentiality has been obtained for the NESARC-III. (Attachment 10)

Law governing Federal employees conducting this survey, 18 U.S.C. 1905, is also relevant to the maintenance of confidentiality of NESARC-III data. Law 18 USC 1905 prohibits disclosure of individuals' identifying information or confidential statistical data by Federal employees.

Disclosure of Confidential Information Generally

> "Whoever, being an officer or employee of the United States or of any department or agency thereof, a person acting on behalf of the Federal Housing Finance Agency, or agent of the Department of Justice as defined in the Antitrust Civil Process Act (15 U.S.C. 1311-1314), or being an employee of a private sector organization who is or was assigned to an agency under chapter 37 of title 5, publishes, divulges, discloses, or makes known in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or related to the trade secrets, processes, operations style of work or apparatus, or to the identity, confidential statistical data; amount or source of income; profits, losses, or expenditures of any person, firm, partnership, corporation or association; or permits any income return or copy thereof or any book containing any abstract or

> particulars thereof to be seen or examined by any person except as provided by law; shall be fined under this title, or imprisoned not more than one year, or both; and shall be removed from office or employment."

All respondents will be informed of the sponsor, the nature, purpose and uses of the survey data, legal authorities, the voluntary nature of the survey and the absence of penalties for non-participation, and the protection of the information in an advance letter (Attachment 8) mailed to all dwelling units one to two weeks prior to the data collector's visit. Prior to administration of the screener, the data collectors will ask if the household received the introductory letter. Those respondents who do not recall receiving or reading the letter will be provided with a copy of it and sufficient time will be allowed for them to read it and ask any questions related to it.

Respondents will be assured of the privacy of their responses. Unique study identifiers will be assigned to each sample person and will be used to link responses to the AUDADIS-V and the DNA specimen collection. **The sample person's identifying information will be destroyed within about four weeks after their participation in the NESARC-III when it is no longer needed for verifying the link between phenotypic data and genetic samples. NIAAA will not have access to identifying information prior to its destruction by Westat. Westat will be transferring all NESARC-III data and associated products and documents to NIAAA at the time of compiling final data files and will not retain ANY records of the NESARC-III.**

Personal identifiers will not be included in the data received by NIAAA and no NESARC-III data is retrieved by any personal identifiers.

As noted previously, a PIA has been promoted for the NESARC-III. (Attachment 6) The Privacy Act System of Records Notice (SORN) Number is 09-25-0200. (Attachment 11)

NESARC-III has also undergone review and received approval from the NIH and Westat Institutional Review Boards (IRBs) and documentation of those reviews is provided in Attachment 12. All consent documents have also been interleaved into the Flow Diagram of the NESARC-III Interview appearing in Attachment 8.

Information on the consent document, related to the AUDADIS-V interview and collection of the saliva sample (Attachment 8) is presented in language that is easily understood and covers many topics, including the (1) voluntary nature of the data collection; (2) purposes and uses of the data; (3) storage and use of the samples; (4) privacy of the information; (5) whether study results or information are available to the respondent; (6) benefits/risks; and (7) contact information regarding questions about the survey. Note that personal identifying information will be destroyed after data collection (i.e., there will also be no coded information that links the respondent's information to identifiers).

The data collector will implement the consent procedure for the AUDADIS-V interview and saliva collection by reading the document verbatim from a computer screen, while at the same time the respondent receives a copy and reads along with the interviewer. After reading the document and answering any respondent questions, the data collector will confirm the respondent's decision to participate by striking a "1" (for yes to the interview and saliva collection) or "2" (for yes to the interview only) or "3" (for decision not to participate at all) in the computer application. This electronic documentation remains a permanent part of the respondent's information. (See Attachment 8 for overview of NESARC-III Interview flow.)

A.10b Storage and Disposition of the Information

At the NIH, there is a detailed policy for sharing data obtained by NIH-supported genome-wide association (GWAS) or sequencing studies. NIAAA is planning to conduct a sequencing study using NESARC-III

data. NIAAA will be expected to deposit the results of the NESARC-III genome-wide scan (gene frequencies) into a central data repository (called dbGaP) which is also to include a subsample of phenotypic (questionnaire) data. NESARC-III data submitted to dbGaP will be stripped of personally identifying information and subjected to disclosure limitation procedures prior to its submission to dbGaP. The dbGaP repository is governed by a Senior NIH Oversight Committee. Researchers requesting to conduct analyses of data in dbGaP must apply to one of several NIH Data Access Committees (DACs) that are formed by NIH staff with particular interests in the data being collected. After review of a Data Access Request, a Data Use Certification (DUC) must be signed by the Investigator and an Institutional Official to document their joint agreement to follow NIH policy for the use of GWAS data obtained from the NIH data repository, the dbGaP. Stipulations included in the DUC include prohibition against sharing the data with anyone other than individuals listed on the Data Access Request, agreement not to attempt to identify individuals from whom the data were obtained, and annual progress reports on research using the GWAS dataset. (See Attachment 13 for GWAS and Attachment 14 for dbGaP policies including those that relate to protection of privacy of the records it maintains). In addition to providing data to dbGaP, NIAAA will be developing its own data repository and data disclosure, sharing and confidentiality plans that apply to researchers collaborating directly with NIAAA to analyze the NESARC-III data.

The provisions for access and security of data placed in dbGaP are rigorous within the context of the privacy laws under which it operates. (See also Section A.10a). It is the responsibility, however, of the NIAAA Principal Investigator of the NESARC-III to provide data to the NIH dbGaP and NIAAA collaborating researchers that have passed its rigorous procedures for protection of confidentiality. NIAAA defines confidential information as any identifiable information about a person collected under an assurance that restricts the degree to which the information can be shared with others. Identifiable information refers to information that can be used to establish an individual’s identity,

whether directly – using items like name, address, etc. – or indirectly – by linking data about respondents to external data that directly identify them. As mentioned, all identifiable information will be destroyed once the phenotypic and genotypic data are linked. It is important to understand that information which by itself would not lead to the identity of a respondent, but which could do so if combined with other data elements or with data already available or released (e.g., the identities of areas in which a survey was conducted) must also be considered confidential.

A key component of NIAAA's Data Confidentiality Plan is the establishment of a Data Disclosure Review Board with the following responsibilities:

- Review electronic data products subject to limited access release by consulting and implementing relevant and sound principles of statistical disclosure limitation as recommended by OMB: the Confidentiality and Data Access Committee's Check List on Disclosure Potential or Proposed Data Release and Statistical Working Paper 22, Report on Statistical Disclosure Limitation Methodology.

- It is anticipated that geographic places with fewer than 100,000 persons will not be identified for any limited access data file and that alternatives to providing information on PSUs (necessary for statistical analysis of the NESARC-III data) will be strongly considered, for example, providing for replicate weights.

- Most if not all analyses of the NESARC-III phenotypic and genotypic data will be restricted to limited access data files. Limited access data files will undergo disclosure limitation procedures that do not perturb the integrity of the research data for the scientific purposes for which it was collected. The Micro Agglomeration, Substitution, Subsampling and Calibration (MASSC) or related procedures will be used. Although standard procedures of categorization and top- and bottom-coding are necessary (agglomeration), uncertainty perturbations including substitution, subsampling and calibration procedures will be empirically assessed based on the nature of the data and the impact of such procedures on the scientific integrity of the data.

- MASSC and related procedures have been primarily developed for data derived from responses to questionnaires and not the genotypic data themselves. De-identifying genetic data by stripping off direct identifiers (e.g., name, address, birth date, etc.) has been referred to as anonymizing the data. However, recently, new statistical bioinformatic technologies have been rapidly evolving to additionally de-identify the DNA sequence data themselves. At the time the NESARC-III genotype data are received by NIAAA, the best algorithm will be used for anonymizing the collection of person-specific DNA sequences. It is anticipated that algorithms developed to anonymize the genetic data will be available and implemented on the NESARC-III genetic data in a way that preserves the integrity of the data for the scientific purposes and uses for which the information was collected. (See e.g., Malin, An evaluation of the current state of genomic data privacy protection technology, and a roadmap for the future. Journal of the American Medical Informatics Association, 12: 28-34, 2005.)

A data sharing plan between NIAAA and its collaborators is necessary for protecting the confidentiality of the NESARC-III data. A collaborator or collaborating party is one with whom NIAAA has a formal working relationship. A working arrangement can be defined in such documents as a Memorandum of Understanding (MOU), Interagency Agreement (IAG) or contract. Collaborations can also include a consortium of researchers developed within a single institution or across several institutions through grant mechanisms such as collaborative grants (U01s). The U01 mechanism that would be used is the Intramural-Extramural grant designation in which analyses of the NESARC-III information will be shared between NIAAA and institutions and other scientific entities. NIAAA's data sharing plan is an important extension of that provided for in NIH's GWAS/dbGaP.

Regardless of source of collaboration, all collaborators are subject to the same confidentiality laws and regulations governing the NESARC-III data as NIAAA employees. Like dbGaP, any collaborators wishing to conduct analyses on NESARC-III limited access datafiles through any of the mechanisms identified above will apply to the NIAAA Data

Access Committee (DAC). After review of a collaborator's Data Access Request (DAR), a Data Use Certification (DUC) must be signed by the Principal Investigator and the Institutional Official to document their joint agreement to follow NIAAA policy for the use of the NESARC-III data. Stipulations included in the DUC include prohibitions against sharing data with anyone not listed on the DAR and identifying individuals from whom the data were obtained and the provision for annual progress reports and review of analytic products for policy compliance. (See Attachment 15 for Draft NIAAA DUC.)

Westat has also developed many other corporate policies and practices (shared by NIAAA) relating to ensuring and maintaining the privacy prior to, during and after data collection. (See Attachment 16 describing these system policies and practices.) Policies applied to the NESARC-III study include the following.

- All Westat staff who work on NESARC-III sign an Assurance of Confidentiality. (Attachment 17). The Assurance of Confidentiality is a generic form signed by all Westat staff upon joining the company. It is intended to cover all Westat studies and is not tailored to the NESARC-III.

- All staff are required annually to take Westat's Information Security Awareness Training. (NIAAA has a similar requirement.)

- Project data are stored in a limited-access Novell file share. Access is only granted to staff who work on NESARC-III.

- Mobile computers that are used to collect data will employ Full Disk Encryption in compliance with FIPS 140-2 standards to protect against loss or theft.

- Careful procedures are followed by Westat to ensure privacy during the interview, and to protect the privacy of materials generated during the course of the interview. Data collectors are trained to interview respondents in a private area of the dwelling unit.

- All staff at Westat are required to view a confidentiality video and receive documents and material dealing with their responsibilities with respect to confidential information.

- Secure locked access to computer servers and electronic media housing NESARC-III.
- Restricting access to computers and electronic media to those directly included in the conduct of the NESARC-III.
- Use of passwords, encryption and office locks.

A.11 Justification for Sensitive Questions

The major objectives of NESARC-III relate to understanding how environmental and genetic risk factors work together to influence vulnerability to alcohol and drug use and disorders and their associated medical and psychological disabilities. Without asking questions about alcohol and drug use, psychological problems, income, sexual orientation, attraction and preference, childhood adverse events and experiences with traumatic events, that is, questions that relate directly to NESARC-III major risk factors and outcome measures, the major objectives of this study could not be met.

A.11.a Alcohol and Drug Questions

Item nonresponse for alcohol and drug use questions appearing in the Waves 1 and 2 NESARC, identical to those appearing in the NESARC-III, was less than 5.0 percent. There were virtually no reported interview break-offs or refusals to answer the alcohol and drug use and problem questions among the 43,093 respondents.

In numerous household surveys on alcohol and drug use and problems conducted since 1960 in the U.S. it has been demonstrated that such questions have not been considered sensitive by respondents. Item nonresponse for such questions was low (generally less than 5.0 percent), and interview break-offs and refusals related to these questions were negligible (less than 1.0 percent). Those surveys, all of which obtained OMB approval, include the NCHS’s 1979 National Survey of Personal Health Practices and Consequences, the National

Health Interview Survey (NHIS conducted over the past 20 years), the Alcohol and Health Practices Supplement (OMB No. 0937-0021) and its 1988 Alcohol and Health Supplement (OMB No. 0937-0021), the 1985 NHIS Health Promotion and Disease Prevention Supplement (OMB No. 0973-0021), the Substance Abuse and Mental Health Services Administration's (SAMHSA's) National Survey on Drug Use and Health (conducted since the early 1980s), the Bureau of Labor Statistics' National Longitudinal Survey of Youth (conducted periodically since 1973), the Center for Disease Control's (CDC's) Behavioral Risk Factor Surveillance Survey (conducted periodically since 1978), and NCHS's Health and Nutrition Survey I and II and their Epidemiologic Follow-up Study (conducted since 1983).

It is the mission of the NIAAA to determine the causes of alcohol use disorders and their associated disabilities and to develop prevention and treatment strategies for application in the nation's healthcare system. Further, it is a major purpose of the NIAAA to conduct epidemiologic studies to assess the magnitude and risks of alcohol use disorders and their associated disabilities among various subpopulations of the U.S. population. If data were not collected on alcohol use disorders and their associated physical and psychological disabilities in the NESARC-III, the NIAAA could not achieve its mandated mission.

A.11.b Psychological Questions

Alcohol use disorders are associated with an array of psychological problems and conditions including depression and anxiety conditions and several personality traits (e.g., borderline personality traits). These associated disabilities, when co-occurring with alcohol use disorders, adversely impact on severity, course, prognosis, and recovery from each disorder. More importantly, the co-occurrence of alcohol use disorders and numerous psychological conditions influences the duration of the disorders and, treatment-seeking behavior, and impacts on the kind of treatment necessary to ameliorate each

condition. A major objective of the NESARC-III is to identify factors related to unmet treatment need for alcohol services in the general population, an objective that cannot be achieved by focusing on alcohol use disorders alone. The NESARC-III will also go beyond the assessment of treatment need based solely on alcohol use disorders to the assessment of treatment need for conditions that frequently co-occur with them. Further, the overwhelming evidence from the first generation genome-wide association studies (GWAS) has shown that co-occurrence of alcohol and other substance use disorders and other physical and mental conditions share many genes in common. Such overlap that may exist also in the CNVs will be a focus of the gene sequencing objectives of the NESARC-III.

Questions dealing with depression, anxiety and personality traits and disorders, very similar to those appearing in all prior NIAAA surveys since 1991-1992, have appeared frequently in other national surveys of the general population since the early 1980s. These include the National Institute of Mental Health's Epidemiological Catchment Area Survey (ECA), fielded between 1981 and 1985 and its 1990-1992 and 2001-2002 National Comorbidity Surveys (NCSs), supplements to NCHS's National Health Interview Survey in 1983, 1988, and 1991, CDC's Behavioral Risk Factor Surveillance Surveys since 1980, and in 15 NIAAA-supported national surveys conducted by the Alcohol Research Group since 1991. An analysis of all these surveys indicated that questions related to psychological problems and conditions were not considered sensitive by respondents. Nonresponse for these questions was extremely low (i.e., less than 4.0 percent), comparable to questions not normally regarded as sensitive.

NIAAA has developed a handout (Attachment 18) that provides respondents with national help lines for problems with alcohol, drug and mental health issues. This handout will be provided to all sample persons. A similar handout was used in three prior NIAAA national surveys.

A.11.c Income

The personal, family and household income measures collected in the NESARC-III will be identical to those collected in the Waves 1 and 2 NESARC. Income questions were operationalized as open-ended questions, followed by questions with fixed income response categories. When respondents were given a choice of either providing an open-ended response or selecting a category in which their income fell, the response rates for personal, family and household income variables were 89 percent, 90 percent and 98 percent respectively. Nonresponse rates of less than 11 percent indicate that income measures are not as sensitive as believed in the past.

A.11.d Sexual Orientation, Sexual Attraction, and Sexual Preference

NESARC-III respondents will be asked three questions: one on sexual orientation; one on sexual attraction; and one on sexual preference. The rationale for collecting this information is two-fold. First, very little is known about alcohol use disorders and their associated disabilities among gay, lesbian and bisexual individuals in the U.S. Recent small surveys have shown, however, that the rates of these conditions are greater among these subgroups. These questions will serve to fill the gap in U.S. Public Health Statistics on the health of all Americans regardless of sexual orientation. Second, the size of the NESARC-III sample is well suited to estimate the prevalence of individuals with different sexual orientations with more precision than in the past. Moreover, these questions will help track the progress of the Draft Healthy People 2020 objectives to “reduce the number of new AIDS cases among adult men who have sex with men”. Numerous Department of Health and Human Services’ and other surveys over the years have asked these sexual orientation questions and these surveys have been summarized in Attachment 19. Importantly these identical questions were asked on the 2004-2005 Wave 2 NESARC and were

associated with no reported break-offs and low item response rates (<5.0%).

A.11.e Childhood Adverse Events and Respondent's Experiences with Traumatic Events

The NESARC-III, like the Wave 2 NESARC, will collect information on the occurrence of adverse childhood events, including physical, sexual and psychological abuse and emotional neglect occurring prior to the age of 18 years, along with information on the respondent's experiences with traumatic life events that could include rape or other assault. All of these questions were asked in the Wave 2 NESARC and associated with no break-offs and low item non-response (<0.5%).

Although the literature highlights the strong relationships between these adverse childhood events, adult traumatic experiences and alcohol use disorders and their associated disabilities, with respect to phenotypic data, a consistent finding in GWAS was their relationship to these same disorders in a gene-environment interaction. Further elucidating these gene-environment interactions is critical, particularly among important subgroups of the population with a view toward progress in etiology and prevention. The NESARC-III, with its oversampling of Blacks, Hispanics and Asians and its provision for sequencing the whole genome is well poised to examine these relationships, especially as they relate to structural genetic variations (e.g., CNVs and related variants).

The collection of this information will also contribute to monitoring the progress of the Draft Healthy People 2020 objectives to: (1) reduce the rate of rape and attempted rape; and (2) reduce maltreatment of children.

Many, if not all of the aforementioned questions have appeared on numerous other surveys including: (1) the Department of Justice's National Crime Victimization Survey (NCVS); (2) National Institute of

Mental Health's National Comorbidity Surveys (NCSs); (3) CDC's Adverse Childhood Experiences Survey (ACE); and (4) the National Institute on Drug Abuse's Adolescent Health Survey (ADD Health).

A.11.f HIV/AIDS-Related Questions

In the NESARC-III, respondents will be asked about the age at first intercourse, occurrence of HIV, AIDS and associated testing and sexually-transmitted diseases (STDs) in the last 12 months and whether a doctor or other health professional had confirmed the diagnosis. Respondents are also asked about their experiences with injection drug use, needle sharing and having sex with individuals who engage in injection drug use. These questions are important as unprotected sex often occurs during episodes of alcohol and drug use and much more research is needed to understand these relationships if prevention efforts are to be effective. Moreover, collecting these data on the NESARC-III will also significantly contribute to monitoring the Draft Healthy People 2020 objectives related to: (1) reducing AIDS among adolescents and adults; (2) reducing the number of new AIDS cases among adolescent and adult men who have sex with men; (3) reducing the number of new AIDS cases among adolescents and adult men who inject drugs; (4) reducing the number of cases of HIV infection among adolescents and adults; and (5) increasing the proportion of adults and adolescents who have been tested for HIV in the past 12 months.

Most, if not all of these HIV/AIDS questions have been asked in numerous prior surveys, including: (1) the Centers for Disease Control's National Survey on Family Growth; (2) the Centers for Disease Control's STD Surveillance System; (3) the NCHS's (a) National Health Interview (NHIS); and (b) National Health and Nutrition Examination Survey (NHANES); (4) the National Institute on Drug Abuse's Adolescent Health Survey; (5) the Center for Disease Control's Project Mix Sexual Behavior; (6) the Center for Disease Control's Young Men's Study; (7) the National Institute on Drug Abuse's Monitoring the

Future Panel; (8) the National Center for Health Statistics' Youth Risk Behavior Surveillance System (YRBSS); (9) the Substance Abuse and Mental Health Services Administration's National Household Survey on Drug Use and Health (NHSDUH); and (10) the NIAAA's Wave 2 NESARC.

A.12 Estimates of Hour Burden Including Annualized Hourly Costs

Hour burden for the NESARC-III, including the Reliability and Validity components and pilot test is:

Type of Respondents	Number of Respondents	Frequency of Response	Average Time per Response	Annual Hour Burden
Adults-NESARC-III Survey Proper (including pilot test of 100 respondents)	44,900	1	1.0	44,900
Adults-Reinterview, reliability study	1,000	2	.75	1,500
Adults-Reinterview, validity study	700	2	1	1,400
Total	46,600			47,800

Annualized cost to respondents associated with the NESARC-III including the Reliability and Validity components and pilot test is:

Type of Respondents	Number of Respondents	Frequency of Response	Average Time per Respondent	Annual Hour Burden	Hourly Wage Rate	Respondent Cost
Adults-NESARC-III Survey Proper (including pilot test of 100 respondents)	44,900	1	1.0	44,900	$19.60	$880,040
Adults-Reinterview, reliability study	1,000	2	.75	1,500	$19.60	$29,400
Adults-Reinterview, validity study	700	2	1	1,400	$19.60	$27,440

Total	46,600	47,800	$936,880

Burden estimates were based on the empirical results of the Waves 1 and 2 NESARC. The average length of interview was 55 minutes. To be conservative, a one-hour interview administration time was selected to represent our burden estimate for NESARC-III using a survey instrument of virtually identical length and content to that of the Waves 1 and 2 NESARC instruments. This estimate includes the time needed to respond to the entire interview, read the introductory letter, review consent materials and to potentially respond to the data quality verification interview.

The estimate for the hourly wage rate of respondents was arrived at by determining the average hourly wage rate of 34,653 Wave 2 NESARC respondents ($17.60). This estimated hourly wage rate was then adjusted upward by $2.00 (i.e. to $19.60) to reflect cost of living increases and inflation.

A.13 Estimate of Other Total Annual Cost Burden to Respondents or Record Keepers

There is no other annual cost burden to respondents or Record Keepers in this survey. There are no capital, operation or maintenance costs for the NESARC-III.

A.14 Annualized Cost to the Federal Government

The total estimated cost of this survey to the Federal Government is $56,431,116.00 (including incentive payments). The total estimated cost is distributed between FY 2009 and FY 2015 as follows: FY09, $381,044.00; FY10, $4,942,575.00; FY11, $7,304,102.00; FY12, $22,039,432.00; FY13, $17,097,928.00; FY14 $2,429,552.00; and FY15, $2,236,483.00.

Westat will receive $42,831,116.00 from NIAAA through a contract during FY10-FY15. The DNA repository will receive $12,000,000.00 from NIAAA through a contract during FY12-FY15.

The method used by NIAAA to arrive at the total estimated costs of this data collection activity consisted of a detailed analysis of the NIAAA's survey requirements in computerized comparison to the costs actually incurred in the most recent prior NIAAA survey, the Wave 2 NESARC (adjusting for cost of living and inflation). Westat's costs of information collection include: sample design, verification, and maintenance; survey planning and management; questionnaire computerization; forms design and printing; preparation of data collector training materials; data collector training; all data collection; data collector observation and quality control procedures; preparation of edit and imputation specifications; data verification; development of data processing systems; weighting of the survey data; and salaries and travel. The DNA repository costs include costs related to receipt of saliva samples, DNA extraction, quality testing of DNA samples, freezers, plating, storage and distribution of DNA for sequencing.

The remaining $1,600,000.00, an estimated $200,000.00 for each year (FY2009-FY2015), is applied to NIAAA's survey operations. These figures represent supervisory, analytic, programming, and secretarial time related to questionnaire development and data collector observation and training materials, statistical design and analysis, and publication of survey data. When viewed in terms of survey person years, these figures represent an average of two per year over the seven year period. This person year estimate will not require additional recruitment. In the Laboratory of Epidemiology and Biometry, NIAAA, staff effort is directed toward the development and analysis of alcohol epidemiologic surveys, and the NESARC-III is its current major focus.

A.15 Explanation for Program Changes or Adjustments

This is a new collection of information.

A.16 Plans for Tabulation and Publication and Project Time Schedule

A.16.a Plans for Tabulation and Publication

The major objectives of the Wave 2 NESARC presented in Sections A.1 and A.2 of this OMB submission define and direct plans for tabulation, statistical analysis, and publication of NESARC-III data. The first step in the plan is to estimate the prevalence of harmful consumption levels and alcohol use disorders and their associated disabilities (objectives 1 through 3), treatment need and utilization (objectives 4 through 8), and estimation of economic costs (objective 9). Basic prevalence information on NESARC-III outcome variables is critical to defining the current magnitude of the problem in the U.S. population and assessing changes over time (relative to prior NIAAA-conducted surveys serving as baselines).

The second step in plans for tabulation and publication calls for cross-tabulations of the prevalence of major outcome variables (harmful alcohol use and alcohol use disorders and their associated disabilities) across levels of putative environmental and genetic (SNP or other variant frequencies) risk factors that can appear in published articles or reports either as standalone descriptive pieces or as preliminary statistics for more multivariable substantive analyses. An example of a tabulation of selected NESARC-III outcome measure across sociodemographic factors is shown in Table 1 of Attachment 20.

Similarly, allele frequencies and genotype prevalence can be estimated for the detected genetic variants. (e.g., SNPs, CNVs) Table 2 in Attachment 20 shows an example of weighted allele frequency point estimates for each of 3 major race-ethnic subgroups of the U.S. population. Analyses supporting this tabulation include using standard statistical packages to determine deviations from Hardy-Weinberg proportions test with a chi-square goodness of fit approach. Allele

frequencies and genotype prevalence will be calculated on weighted data (inclusive of accounting for NESARC-III design effects) for each gene variant for all major race-ethnic groups. Point estimates and 95% confidence intervals will be calculated and weighted for each race-ethnic group to obtain the nationally representative estimates for the U.S. population. Tests of the difference in allele frequencies among race-ethnic groups will be performed by using polytomous logistic regression. Tests of the differences in genotype prevalence among these groups will be evaluated using the Wald chi-square statistic.

The third analytic step addresses more substantive research questions, requiring multivariable statistical analyses. In these analyses, relationships between environmental and genetic risk factors and harmful alcohol consumption levels and alcohol use disorders and their associated disabilities will be examined. In these multivariate analyses, major outcome variables represent dependent variables, while environmental and genetic risk factors, including major demographic and socioeconomic variables, usually will serve as independent, confounding, mediating or moderator variables. The specific multivariable procedures to be performed on the data primarily will depend on the: (a) basic characteristics of the outcome data (e.g., their continuous or discrete nature); (b) the specific hypothesis or research question being addressed; (c) ability of the data to satisfy the underlying assumptions of the statistical model; and (d) the sample size and power consideration for specific multivariate analyses.

Examples of multivariable analyses using NESARC-III data are shown in Attachment 20 as follows.

Table 3 (Attachment 20) shows logistic regression analyses of alcohol abuse and dependence (outcome variables) with genetic variant DRD2, sex, age, and adult traumatic events and childhood adversity as independent variables. Analyses are conducted separately for individuals with African American and European American ancestry because the frequency of genetic variants differs across ancestry. The analyses also include a pooled logistic analysis across African

Americans and European Americans, an analysis that requires an additional independent variable, that is, ancestry score, to control for variation in allele frequencies across ancestry groups. Note that this analytic procedure will also examine gene-environment interactions between the genotype and environmental factors (e.g., adult traumatic events, childhood adversity).

Table 4 (Attachment 20) shows the preliminary univariate comparisons of several CNR1 allele (or genotype) frequencies between controls and individuals with drug dependence, individuals with alcohol dependence, and individuals with comorbid alcohol and drug dependence among European Americans. Assuming that significant differences in frequencies were found in SNP3 and SNP8 between controls and each of these disordered groups, the next analyses would examine these gene-gene interactions within a multivariable linear logistic regression context (Table 5).

There are numerous parametric and nonparametric multivariable approaches used in gene-disease association studies and these analyses are those typically used in traditional epidemiology. They include analysis of variance, path analysis, linear regression analysis, principal component analysis and other general linear model procedures. A host of software packages, many of which are without cost, exist (and are being continually developed and improved) for association studies. Many of these packages include tests of data quality in terms of inconsistency, sample and genetic variant missingness, fidelity of the genotype assignment for each genetic variant, perturbation analyses, identification of outliers, calculation of degree of inflation, and most importantly, control for population structure (stratification).

A.16.b Project Time Schedule

The following outlines the key activities and time schedules for NESARC-III data collection activity.

Activity	Time Schedule
Complete training materials and computerized instrument	2 Months after OMB approval
Finalize all computerized programs and survey forms	2 Months after OMB approval
Conduct pilot test	3-5 Months after OMB approval
Begin main data collection	14 Months after OMB approval
Process and clean questionnaire data	15-28 Months after OMB approval
Publish preliminary study results/release limited access data for questionnaire	39 Months after OMB approval
Publish preliminary study results/release limited access data files for genetic data	39 Months after OMB approval

A.17 Reason(s) Display of OMB Expiration Date is Inappropriate

This data collection activity does not seek approval not to display the expiration date for OMB.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

This data collection activity does not seek any exception to the certification statement associated with 5 CFR.1320.9, Certification for Paperwork Reduction Act Submissions.