Supporting Statement: Section B

Prevalence of Alcohol and Other Drug Use among Motor Vehicle Crash Victims Admitted to Select Trauma Centers

Background

The National Highway Traffic Safety Administration (NHTSA) is seeking approval to conduct a study that will gather drug prevalence information for a sample of seriously- or fatally-injured roadway users transported to study-selected trauma centers and morgues immediately after their injuries were sustained in a motor vehicle crash (MVC).

There have been recent efforts in the European Union[1] and Canada[2] to improve the knowledge of drug prevalence among seriously injured drivers. The European Integrated Project, Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID) study involved data collection across nine European countries to determine the prevalence of psychoactive substances in the general driving population and drivers who were seriously injured or killed in crashes. The data collection and toxicology methods varied significantly across countries, however, which limits the usefulness of the information. The study in British Columbia, Canada utilized a methodology similar to that being executed for the current study. The Canadian study analyzed blood already collected during the clinical treatment of trauma patients to provide prevalence rates for a variety of drugs in the systems of the injured drivers. The sample size in the Canadian study, however, was relatively small compared to that proposed in the current effort. Additionally, the European and Canadian studies likely have little generalizability to the United States given the different laws and populations of the countries.

For the current study, the participating trauma centers and medical examiners will allow NHTSA's research associates access to de-identified blood samples, when available, that were already collected during their routine clinical treatment for seriously- or fatally-injured patients involved in MVCs. The study will then conduct independent and de-identified drug toxicology testing to determine the prevalence of alcohol and other drugs in the systems of the injured parties. The trauma centers and medical examiners will also allow the study's research associates access to other de-identified standard classification information such as patient demographics, position in crash, and injury nature and severity. The trauma centers and medical examiners will allow access to this already-collected and de-identified information to the study in accordance with all applicable Federal, State, local, and institutional regulations governing the sharing of such information and as approved by the study IRB.

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[1] Hels, T., Bernhoft, I. M., Lyckegaard, A., Houwing, S., Hagenzieker, M., Legrand, S., Verstraete, A. (2011). Risk of injury by driving with alcohol and other drugs. DRUID (Driving under the Influence of Drugs, Alcohol and Medicines).

[2] Brubacher, J., Chan, H., Martz, W., Schreiber, W., Abridge, M., Eppler, J., Lund, A., Macdonald, S., Drummer, O., Purssell, R., Andolfatto, G., Mann, R., & Brant, R. (2016) Prevalence of alcohol and drug use in injured British Columbia drivers. *BMJ Open*, *6*:e009278.

B.1. Describe the potential respondent universe and any sampling or other respondent selection to be used.

The potential respondent universe includes all individuals seriously- or fatally-injured in an MVC who are transported directly to the selected trauma centers and morgues. Drug toxicology analyses will only be conducted when the trauma centers or medical examiners are able to provide an adequate blood sample that was collected during their normal clinical treatment activities but was not used. When no blood is available, only de-identified classification information such as demographics and injury severity will be collected. The classification information for cases that do not have sufficient available blood for toxicology testing will be used to determine if there is any bias in the toxicology data by classification, such as a certain age group (or other demographic category) that may have significantly more or less drug test results available as compared to other age groups.

This prevalence study will be conducting toxicology testing for a wide variety of potentially impairing drugs. This will require a sufficient sample size to be able to identify some of the less prevalent impairing drugs of concern per impaired driving and traffic safety. Our calculations for a sufficient sample size is provided below.

Sample Size Calculations

Sample Acquisition. NHTSA is working with three high-flow Level 1 trauma centers and the associated morgues that service the same catchment areas. They were selected by NHTSA because they each have qualified research staff and high numbers of patients with injuries resulting from motor vehicle crashes. These trauma centers and morgues offer NHTSA a realistic opportunity to gather a large sample size in the shortest time possible. The same data collection protocols will be utilized at each site. All data will be used only in aggregate to calculate drug prevalence among the injured and killed presenting to the trauma centers and morgues.

Sample Size Calculation. For a one-time measurement of prevalence, the equation below is generally used to calculate the sample size needed for a given drug prevalence rate at a specific level of statistical confidence and precision.[3]

$$n = \frac{Z^2 P(1 - P)}{d^2}$$

Z = Z statistic for a level of confidence (e.g., Z = 1.96 for 95% confidence)
P = expected prevalence (e.g., 15% or 0.15 estimated from prior studies)
d = precision (e.g., 3% or 0.03 which provides a confidence interval of $\pm$3%)

The British Columbia, Canada study mentioned above offers insights into possible drug class prevalence rates for drivers presenting to a trauma center in North America. The

[3] Daniel, W.W. (1999). *Biostatistics: A Foundation for Analysis in the Health Sciences.* 7th Edition. New York: John Wiley & Sons.

table below provides the observed drug prevalence rates for the major classes of drugs tested for in that study.

Table 1. British Columbia, Canada Drug Prevalence (N = 1,097)

Drug or Drug Class	Prevalence % (95% CI)
Alcohol	17.8 (15.6 – 20.1)
THC-COOH*	12.6 (10.7 – 14.7)
Delta-9 THC	7.3 (5.9 – 9.0)
Cocaine	7.2 (5.8 – 8.9)
Opiates	4.8 (3.7 – 6.3)
Benzodiazepines	4.0 (2.9 – 5.3)
Amphetamines	2.3 (1.5 – 3.3)

*Metabolite indicating marijuana use.

If a study wanted to have 95% confidence with an expected individual drug prevalence rate of 15% and 3% precision it would need 545 participants as shown in the calculation below. Given the drug prevalence rates shown above from the Canadian study, this sample size would only be sufficient if the study wanted a reliable estimate for alcohol.

$$n = \frac{(1.96)^2 (.15)(1 - .15)}{(.03)^2} = 544.23 \text{ or about } \mathbf{545} \text{ participants}$$

If the expected prevalence rate is lower, as it surely is for drugs other than alcohol, a more precise estimate is generally advisable, and the sample size can increase dramatically. For example, if you wanted to have 95% confidence in a study with an expected prevalence rate of 7% and 1% precision you would need 2,501 participants as shown in the calculation below.

$$n = \frac{(1.96)^2 (.07)(1 - .07)}{(.01)^2} = 2{,}500.88 \text{ or about } \mathbf{2{,}501} \text{ participants}$$

Special considerations are needed when prevalence rates are expected to be very low or high.[4] The table below provides the sample sizes needed for low prevalence rates at various levels of precision. These calculations demonstrate that getting precise estimates for low prevalence drugs will take a relatively large sample if a high degree of precision is desired. For example, if the expected prevalence rate is .02 (2%) and a precision of .005 was desired, the study would need a sample size of 3,012.

Table 2. Sample Size Needed for Low Prevalence Drugs

Precision	Prevalence				
	.01	**.02**	**.03**	**.04**	**.05**
.005	1522	3012	4472	5901	7299
.01		753	1,118	1,476	1,825

[4] Naing, L., Winn, T., & Rusli, B.N. (2006). Practical issues in calculating the sample size for prevalence studies. *Medical Statistics, 1,* 9-14.

.015			497	656	811
.02				369	457
.025					292

Based on the above calculations, and drug prevalence rates observed in prior studies, the current effort is proposing to gather data from a total of 7,500 people injured or killed in motor vehicle crashes. Over half of these patients are expected to be drivers (N = 3,750). This sample size will allow for precise drug prevalence calculations (i.e., narrow 95% confidence intervals) among drivers for even the very low prevalence drug classes. Drug prevalence rates for other types of road users (e.g., pedestrians, bicyclists, scooters) with smaller sample sizes will have wider confidence intervals, but sample sizes will be sufficient for most classes of road users to provide a reasonable picture of drug prevalence among each.

Statistical Analysis Plan

The primary objective of this project is to report the observed prevalence of drugs in seriously- and fatally-injured drivers and other motor vehicle crash-involved persons directly transported to the selected trauma centers and medical examiners. As such, observed drug prevalence rates and 95% confidence intervals will be calculated for each road user type (e.g., drivers, pedestrians, scooter riders, pedestrians). Further breakdowns by subgroups within classification variables (e.g., by age group, sex) will be reported to the extent sufficient sample sizes are available. The proposed sample size should be more than sufficient for these prevalence calculation purposes for many, if not all, of the drugs being examined. Other descriptive statistics such as average blood concentrations will be reported to the extent enough reliable data exists for each individual drug or class of drugs. Prevalence rates will be calculated for the three catchment areas for the three participating trauma centers and corresponding morgues only. No inferences will be made to populations beyond the three trauma center areas.

B.2. Describe the procedures for the collection of information.

The participating trauma centers and medical examiners have agreed to provide de-identified blood samples and other de-identified patient classification information that was already collected during the application of their normal clinical procedures. As such, this study will not have any contact with patients and will only utilize information made available by the trauma centers and medical examiners after treatment is complete. This study is operating under a waiver of consent and authorization as approved by the study IRBs. Under these waivers, the participating trauma centers and medical examiners can provide the de-identified samples without obtaining patient consent and authorization so long as the information is adequately de-identified as planned.

The general study flow for crash-involved drivers and other roadway users at the participating trauma centers and medical examiners is as follows:

- Crash occurs / EMS on scene

- Triage by EMS or at Emergency Department
- Seriously-injured sent to trauma center and trauma team activated; fatally injured sent to morgue
- Trauma center or medical examiner staff member treats patient per standard procedures, and collects blood samples and patient information for clinical purposes (extra blood samples are routinely collected and stored)
- After the trauma center or medical examiner has concluded treatment or autopsy activities, the blood collected during normal clinical procedures and associated information are given randomly-generated case numbers, and stored for research purposes by the trauma centers or medical examiners

After the above flow of events is completed, our study research associates then

- Identify MVC victims as eligible for the study through the de-identified records
- Collect the de-identified blood sample, when available, and other de-identified classification information for MVC victims
- Send the blood sample to independent laboratory for toxicology testing

In all cases, following their normal treatment procedure, the trauma centers and medical examiners will obtain blood samples for clinical purposes as a patient presents to the center or morgue. The blood samples, when available after all clinical treatment is complete, can be provided to the study under the waiver of consent approved by the reviewing IRB. Language on the appropriateness of the waiver of informed consent is provided below from the United States Department of Health and Human Services (HHS) web site and as outlined under the Common Rule which applies to the Department of Transportation with the same language under 45 CFR Part 11.[5] The HHS-approved IRB(s) granted the waiver of informed consent because the IRB determined the study met these requirements for the waiver.

> *Waiver or alteration of the requirements for obtaining informed consent from adult subjects can occur under any of the following three provisions:*
>
> *2. Research in general: an IRB may waive or alter the requirement of informed consent under 45 CFR 46.116(d), provided that the IRB finds and documents that all of the following four conditions are met:*
> - *the research involves no more than minimal risk to the subjects;*
> - *the waiver or alteration will not adversely affect the rights and welfare of the subjects;*
> - *the research could not practicably be carried out without the waiver or alteration; and*
> - *whenever appropriate, the subjects will be provided with additional pertinent information after participation.*

The trauma centers are also authorized to release the blood, demographic, treatment, and injury information under a waiver of HIPAA authorization as granted by the reviewing

[5] https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html

IRBs – Advarra[6] and University of Florida. HHS and Department of Transportation regulations provide for waivers in this situation.[7] The applicable wording is:

> *The following three criteria must be satisfied for an IRB or Privacy Board to approve a waiver of authorization under the Privacy Rule:*
>
> 1. *The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:*
> - *an adequate plan to protect the identifiers from improper use and disclosure;*
> - *an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and*
> - *adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;*
>
> 2. *The research could not practicably be conducted without the waiver or alteration; and*
> 3. *The research could not practicably be conducted without access to and use of the protected health information.*

The trauma centers and medical examiners will temporarily store all blood samples in secure refrigerated storage on their premises, identified only by a randomly-generated study tube number – there will be no information that could potentially be used to identify the victim. This de-identification process is routinely done for research studies at the trauma centers. The samples will be collected by study research associates and sent in batches directly from the trauma centers and medical examiners to the study's independent toxicology laboratory for testing for the presence of drugs. The toxicology laboratory will not have access to any study database other than their own which will house the toxicology results stored by study tube number.

The trauma centers and medical examiners have authorized our research associates to access patient records to gather the needed classification information (e.g., age, sex, position in crash). The research associates will manually enter the de-identified information into the study tablet system by a study- specific participant ID. All toxicology results will be transmitted from the study laboratory directly to the main study database for storage. No toxicology results will be sent back to the participating trauma centers/hospitals or morgues, and the toxicology results will never be included in participant medical records. The study data system will then merge the toxicology and participant classification information using the study ID and blood tube numbers to create a de-identified analysis record.

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[6] Previously known as Chesapeake IRB.

[7] 45 CFR 164.501, 164.508, 164.512(i) as reported in https://www.hhs.gov/hipaa/for-professionals/privacy/guidance/research/index.html

The study protocols have been carefully designed and reviewed to prevent any linkage to an individual participant. As such, it will be impossible for anyone to link toxicology results to a given individual. In addition, there will be no records of who had access to or handled the various samples at any given time, and they will be unsupervised in the refrigerator before they are sent for analysis. As such, the chain of custody will be broken thereby further precluding any interest in the de-identified data for use in legal proceedings.

B.3. Describe methods to maximize response rates.

The participating trauma centers already routinely collect blood samples, injury information, and classification information for every patient when a trauma alert is activated. Trauma alerts are activated when the transporting EMS staff or the other treating medical staff determine the patient meets trauma alert criteria.[8] Even if these criteria are not met but EMS brings the patient to the trauma center, the treating professional can activate an alert if he or she suspects a serious injury may have occurred that is not currently presenting.

As noted above, under a waiver of consent and waiver of HIPAA authorization, which has been granted by the reviewing HHS-approved IRBs, the trauma teams will provide to the study a de-identified blood sample, when available, for every patient injured in an MVC who has a trauma alert activated. This process provides the best opportunity to gather information on the universe of seriously injured road users in a given area. If a blood sample is not available for an eligible patient, the study will still collect available classification information to provide information on possible sample biases.

For fatally-injured drivers, blood samples are routinely gathered for the medical examiner's own testing/autopsy purposes. The medical examiners have agreed to provide blood samples, when available, after all post mortem procedures have been completed, as well as classification information to the study under the same waivers of consent and HIPAA authorization.

[8] See http://ems.ufhealthjax.org/uf-health-jax-trauma-criteria/ for an example of the criteria used by one of the participating trauma centers/hospitals.

B.4. Describe any tests of procedures or methods to be undertaken.

We will pilot test all protocols at each trauma center. We do not anticipate substantive changes to the methodology outlined in this document as all procedures have been thoroughly reviewed with each center and conform to their current standard operating procedures.

NHTSA has experience obtaining sensitive data, including biological samples. The participating trauma medical staff have experience conducting research within their centers and providing de-identified samples and information to others for research purposes, and the contractor has experience in obtaining similar data for NHTSA. All participating entities are sensitive to the environment in which data collection will occur and will respond with modest changes as needed to meet the target sample size and data quality requirements.

B.5. Provide the name and telephone number of individuals consulted on statistical aspects of the design

The following individuals have reviewed technical aspects of this research plan:

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