Supporting Statement: Section B

Crash Risk Associated with Drug and Alcohol Use by Drivers in Fatal and Serious Injury Crashes

Background

The National Highway Traffic Safety Administration's (NHTSA) mission is to save lives, prevent injuries, and reduce traffic-related health care and other economic costs. One area receiving much current attention is the study of drug use and driving. Interest has intensified as states legalize use of marijuana for recreational or medicinal purposes. States and other federal agencies look to NHTSA for information on the safety impact of consuming a drug and then driving a motor vehicle, because such behaviors may increase with fewer legal restrictions on marijuana and increased use of prescription drugs. In March 2018, the NHTSA Deputy Administrator held a summit on the drug topic with a "Call to Action" for our agency and our partners to look for new ways to prevent driving after the use of impairing drugs in order to reduce crashes, and to save lives.

NHTSA's Office of Behavioral Safety Research has conducted a range of studies examining all aspects of traffic safety, including the impairing effects of drugs, prevalence of drug-positive drivers, field tests for law enforcement to use in the detection of drug-impaired driving, evaluations of drug-impaired driving laws, and the impact on the criminal justice system. A key component of our research strategy is examining whether drugs (over-the-counter, prescription, and illegal; and also alcohol) increase a driver's risk of being in a crash, and if so, which drugs create the most risk. This is a continuing topic of discussion for senior management testifying before Congress, meeting with state representatives, and working with law enforcement agencies to decrease impaired driving.

Although there are decades of research on the impairing effects of alcohol and a clear relationship between blood alcohol concentration (BAC) and level of impairment, the same is not true for the hundreds of drugs that exist and may be in use by a driver.[1] There are also breath test devices that are used at roadside to determine a driver's BAC and infer level of impairment. For a person who has consumed a drug and then drives, however, no way exists to measure their level of consumption of that drug or the extent of impairment. NHTSA must examine the issue of drug impaired driving using other strategies. The "National Roadside Studies" have estimated the prevalence of alcohol and drug use among drivers on the road, but those studies are not designed to address the issues of impairment or crash risk.

[1] Compton, R. (2017, July). Marijuana-Impaired Driving - A Report to Congress. (DOT HS 812 440). Washington, DC: National Highway Traffic Safety Administration.

In 2016, NHTSA released the results of our "Virginia Beach Crash Risk" study.[2] This was the first large-scale study of drugs and motor vehicle crashes in the United States and was ground-breaking research in the area of drugs and driving. It used a case-control methodology to take a first look at the crash risk of various drugs. The design included obtaining anonymous and voluntary breath, oral fluid, and blood samples from crash-involved drivers in Virginia Beach, Virginia across the 20-month study period. The research teams also obtained anonymous and voluntary breath, oral fluid, and blood samples from recruited drivers at the same crash locations a week later, at the same time of day, and the same direction of traffic – thus controlling for as many factors as possible – and then matching the results of the tests of biological samples from the crash-involved drivers to the non-crash involved drivers. Examining the data required going beyond the initial basic analyses and conducting more sophisticated statistical analyses. The initial analysis provided the odds ratio of a crash if a person tested positive for a single drug or combination of drugs. These unadjusted analyses suggested *increased* crash risk for some drugs, including marijuana. However, when additional variables known to be associated with elevated crash risk (e.g. driver age and sex) were included, along with the presence of alcohol in a person's system, the results indicated there was *no statistically significant increase* in crash risk for any drug other than alcohol. These findings illustrate the importance of collecting basic-level demographic information for use in additional analyses. Without our additional analyses, different conclusions would have been reached and resulted in very different policy implications.

Use of this methodology to examine crash risk (with alcohol only) began with Borkenstein's landmark "Grand Rapids Study" in 1964.[3] This was the first study in this area to use case control methodology, that is, with the use of crash-involved drivers matched to non-crash-involved control drivers. The results provided compelling evidence that moderate BAC levels were associated with increased crash risk, and that risk grew exponentially at BACs of 0.10 g/dL or higher.[4] Following from Borkenstein's initial work, NHTSA used a similar approach to again examine the crash risk of alcohol between 1996 and 1998 in Long Beach, California, and Fort Lauderdale, Florida. This study confirmed the results of the Grand Rapids Study using modern data collection and statistical techniques.[5] These case control crash risk studies were key components in the body of research that led U.S. legislators to encourage (and later mandate) States to lower their BAC limits to .08 (from .10 or higher), to strengthen other impaired driving laws, and to increase enforcement efforts, implement enhanced sanctions, and to develop additional prevention programs.

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[2] Lacey, J. H., Kelley-Baker, T., Berning, A., Romano, E., Ramirez, A., Yao, J., ,… & Compton, R. (2016, December). Drug and alcohol crash risk: A case-control study (Report No. DOT HS 812 355). Washington, DC: National Highway Traffic Safety Administration.

[3] Borkenstein, R. F., Crowther, R. F., Shumante, R. P., Ziel, W. B., & Zylman, R. (1964). *The role of the drinking driver in traffic accidents*. Bloomington, IN: Department of Police Administration, Indiana University.

[4] Borkenstein, R.F., Crowther, R.F., Shumate, R.P., Zeil, W.W., and Zylman, R. (1974). The role of the drinking driver in traffic accidents, 2nd e. *Blutalkohol; Alcohol, Drugs and Behavior*, 11 (Supplement 1).

[5] Blomberg, R. D., Peck, R. C., Moskowitz, H., Burns, M., & Fiorentino, D. (2005). Crash risk of alcohol involved driving: A case-control study. Stamford, CT: Dunlap & Associates, Inc.

Case control methodology is critical in studies of this nature, and is widely used throughout public health and epidemiological research by examining the risk (frequency) of an action or condition, compared to the risk (frequency) of not conducting that action or having that condition. The results provide the relative risk of having an outcome when the person is exposed to the risk factor. Because the case-control design is a retrospective examination of factors impacting the case drivers (i.e., after they have already crashed), it is limited in the extent to which signal can be manipulated. This is because a case-control study does not involve the recruitment and random assignment of participants to treatment groups, has no control over participants' responses to the factor of interest, and does not control the potency of the influencing factor (i.e., drug) of interest. In effect, there is no treatment such as that found in randomized control trial. The experimental group characteristics are determined by the conditions under which the sample is acquired. Thus, the case-control study can dictate a number of relevant factors/events that are measured for participants and the validity of those measures.

In this study, the outcome variable of interest is a driver being seriously injured in a motor vehicle crash, and the risk factor is the presence of one of the tested-for drugs being present in the driver's system. To determine presence of a drug of interest in the driver, the participating trauma centers and medical examiners will provide de-identified blood samples from crash-involved drivers, and NHTSA contract personnel will gather equivalent samples from control drivers near the location of the crash one week later at the same time of day, and in the same direction of travel.

The current study will be testing for numerous potentially impairing drugs using state-of-the-art toxicology testing methods. Also the study's selection criteria allow for the inclusion of only seriously- or fatally-injured drivers which should, in theory, increase the baseline rate of the case drivers having one or more of the drugs of interest in their systems compared to earlier studies which included all levels of crash severity with most being low severity crashes. This relies on the assumption that these severe crashes are more likely to occur when a person is drug-impaired and loses control of the vehicle, or commits some other critical driving error that leads to a violent crash in which the driver is seriously injured.

This study will minimize noise by using identical data collection procedures at each location and analyzing blood samples that the trauma centers collected as soon as possible after a crash. These methodological steps will increase confidence that a given drug was present in the driver's system at the time of a crash. The study will document any drugs administered by EMS and/or the trauma teams before a blood sample is taken to further reduce noise. Additional driver demographic information will be collected and used as part of covariate analyses to further reduce uncertainty that an observed effect was due to a factor other than the drugs of interest. Noise will also be reduced by matching control sampling sites to the crash sites in terms of location, time of day, day of the week, and direction of travel. The control sampling will take place exactly one week after a crash whenever possible. This approach will eliminate noise associated with differences in driver populations due to roadways traveled, traffic conditions, time of day/day of week, and seasonality. Finally, the IRB(s)-approved waiver of consent ensures

that participation rates will be near 100% for injured case drivers given the study approach, which eliminates much potential noise for this group. The only drivers who will not be participants are those for who the trauma center is unable to provide a blood sample (e.g., venous access could not be obtained for treatment; could not determine if the person was a driver). Based on NHTSA past studies with similar protocols, we expect strong participation rates for control drivers, which will reduce noise. We anticipate driver participation rates (for those drivers who enter the research bays) will be 50% or higher based on prior efforts and recent pilot testing.[6] While there may be some remaining noise for the control sample, the participation rate for a study of this type is acceptable. Also, valuable information such as sex, vehicle type, and, possibly, BAC will be available for non-participants thereby further reducing noise.

This approach will provide matched cases that will allow for a calculation of a risk estimate for each class of drugs and, in some cases, for individual drugs with greater prevalence such as alcohol and marijuana. With this information, NHTSA and our Federal partners can develop policies and countermeasures for drugs that represent a true increase in crash risk, rather than focusing on drugs that are typically presumed to be a risk factor without supporting evidence.

For NHTSA, this type of data collection is crucial for learning about the relationship between drug use and crash risk, as the bodily specimen data is completely objective because it comes directly from drivers in crashes shortly after the crash event when any drugs are still present and have not yet been metabolized by the body. However, relative risk can only be estimated if we obtain the same data from matched controls. The findings will allow us to focus countermeasure efforts on the drugs that present the most risk.

NHTSA is conducting this Crash Risk study as the next progression of our research in this area to learn about how drug use plays a role in severe injury crashes. The Borkenstein and Dunlap studies sought information on the risk of alcohol use and driving. With the Virginia Beach study, we could use newly developed oral fluid collection devices, and explore the feasibility of obtaining blood samples at roadside to examine the risk of drugs other than alcohol. In the Virginia Beach study, the vast majority of participants (drivers) were involved in crashes that included damage to the vehicle but no major injury to the driver. While 33% of the crashes involved some type of a driver injury, the injuries typically were not serious and less than 1% involved a driver fatality. These studies all represented crashes in general, but did not allow for an in-depth examination of the most severe crashes where a driver is seriously or fatally injured.

For the current study, NHTSA is collaborating with Level I trauma centers who routinely collect blood samples from injured crash-involved drivers shortly after the crash. Seriously injured drivers are a large percentage of trauma center patients, and blood is drawn for treatment purposes. Because it is not known how many medical tests will be run for a given patient, more blood is drawn than is generally needed. While the blood draw methods may vary slightly by center (some initially fill a single large syringe

[6] See for examples, the studies cited in footnotes #2 and #5.

while others fill smaller, individual tubes directly), a residual sample is almost always available for research purposes. This de-identified sample can be used for research purposes under the Common Rule[7] that regulates the use of biological specimens in federally funded research. In fact, part of a Level 1 trauma center's mission is to engage in research. This is an important factor in being a Level 1 center versus a Level 2 center.[8] An example of related Level 1 research was a study to determine the incidence and prevalence of alcohol and other drug use among motor vehicle crash victims, but this study did not use a case-control design to assess the risk of being severely injured.[9] Similarly, the medical examiners collect blood for autopsy purposes and residual blood is available for research purposes. The participating trauma centers and medical examiners have agreed to provide these de-identified samples of blood and de-identified information (e.g., demographics, drugs administered prior to arrival, crash location) to the study.

This study brings together the ability to obtain a de-identified blood sample previously collected from drivers shortly after a crash and anonymously obtained samples from drivers recruited on the same roadway where the crash occurred. This collaboration of efforts allows for the best investigation into the relationship of drugs to the risk of being seriously or fatally injured in a motor vehicle crash, and providing NHTSA, other Federal agencies, and States with information they need develop data-driven prevention and enforcement programs for key drugs of interest.

As with Virginia Beach, this study is examining the relative risk associated with over-the-counter, prescription, and illegal drug use by studying drivers in crashes.[10] We are testing for 64 drugs that fall into the following classes:

- SSRIs[11] and (5)
- Tricyclics (5)
- Cannabinoids (3)
- Methadone (2)
- Opiates (3)
- Opioids (11)
- Barbiturates (3)
- Benzodiazepines (9)
- Muscle relaxants (3)
- Sleep aids (1)
- Amphetamines (6)
- Cocaine (3)

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[7] Department of Health and Human Services (January 19, 2017). Federal Policy for the Protection of Human Subjects: Department of Transportation 49 CFR Part 11. *Federal Register, Rules and Regulations. Vol. 82, No. 12*; pp 7149 – 7274.

[8] http://airmedical.net/resource/trauma-center-levels-explained, accessed April 5, 2018

[9] Walsh, J. M., Flegel, R., Cangianelli, L. A., Atkins, R., Soderstrom, C.A., & Kerns, T. J. (2004). Epidemiology of alcohol and other drug use among motor vehicle crash victims admitted to a trauma center. *Traffic Injury Prevention*, *5*(3), 254-60.

[10] Much of the control sampling methodology follows the Virginia Beach study model. The technical report, including a full description of the methodology and protocol are attached.

[11] selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors

- Antihistamines (3)
- Cough suppressants (3)
- Street drugs (3)
- Alcohol (1)

These drugs have been selected because they can have impairing effects; are known to be present in toxicology reports of drivers who were arrested for impaired driving, who were involved in fatal crashes; and they were present in drivers in NHTSA's recent National Roadside Study.[12] Any drugs that were not found in previous studies were excluded from the current effort. The selection of drugs was also reviewed by the trauma doctors participating in the study with some new drugs added that the doctors are now seeing in their trauma patients. The ability to test for each of these drugs within a small sample of blood was confirmed with the toxicology laboratory.

As mentioned above, as a driver enters a participating trauma center the medical team extracts blood samples for use during treatment. The trauma centers indicated that more blood is drawn than is usually needed, and de-identified samples can be made available for research purposes along with other de-identified patient information (e.g., demographics, drugs administered prior to arrival, crash location) under the Common Rule. Similarly, the medical examiner can make de-identified samples and information available for research. This method of sample collection for research is not novel. The samples are being collected under routine procedures for the collection of blood for clinical care. The risks, benefits and ethical considerations of the study have been carefully weighed by the investigators, research staff, and two IRBs which have both approved the study. It is common for Level I trauma centers to collect residual blood for research purposes. In this study, the samples are being collected under IRB-approved waivers of consent. All blood samples for this study will be stored in color-coded tubes specific to this study, and trauma center staff will ensure each sample is fully de-identified prior to it being available for this study. This will protect patient privacy, and will reduce burden on the participant population. This process, and human subject protections were discussed with the IRB at length prior to approval.

One week later on the same day of the week, same time of day, and same direction of traffic, a research team, including a phlebotomist will conduct data collection for the control drivers. Recruited drivers will be requested to voluntarily participate, and for those who consent the phlebotomist will request a small blood sample. These control drivers will also be asked to provide a breath test (allows us further information about the presence of alcohol) via a preliminary breath test device, and to answer questions including demographic information, trip information, and opinions about driving while using alcohol or drugs. All data from control drivers will be anonymous. If the data collector believes that the driver is impaired for any reason, the study's protocol includes several strategies to get the person home safely with no involvement of law enforcement and no cost to the driver.

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[12] Kelley-Baker, T., Berning, A., Ramirez, A., Lacey, J. H., Carr, K., Waehrer, G., Compton, R. (2017, May). 2013-2014 National Roadside Study of alcohol and drug use by drivers: Drug results (Report No. DOT HS 812 411). Washington, DC: National Highway Traffic Safety Administration.

The trauma centers and medical examiners will provide data for a minimum of 2,500 crash-involved drivers and field teams will gather data from at least 5,000 control drivers – 1:2 matched design. Data collection will occur in three Level 1 trauma centers and the associated medical examiners. Each of these centers has a large catchment area and routinely receives large numbers of people involved in motor vehicle crashes.

Each trauma center, including their research and administrative offices, has agreed to participate and they have been involved in planning and the development of protocols for obtaining de-identified blood samples. NHTSA is also working with the approval of law enforcement agencies in each of these sites, and their management have been involved in planning meetings.

This study's design and protocols were approved by a central IRB for the trauma center data collection efforts in Charlotte and Miami, and control sampling activities at all three sites (Chesapeake, Pro00022129, November 2917). The University of Florida Health Jacksonville opted to have its local IRB review the protocol for its trauma center data collection activities. The local University of Florida IRB approved the protocols for trauma center data collection and providing of de-identified samples and information to NHTSA (UF IRB201800117). Each participating trauma center's research staff have also reviewed the protocols along with any other required IRB or research committee reviews that must be completed before the data collection is allowed to take place.

The anticipated general participant flow for both crash-involved and control drivers is as follows:

CRASH-INVOLVED DRIVERS	CONTROL DRIVERS
• Crash occurs / EMS on scene • Triage by EMS or at trauma center • Seriously injured driver sent to trauma center for treatment; fatally injured sent to morgue • De-identified blood sample provided by trauma center or ME	• Recruit driver from free-flowing traffic and request consent • Survey driver • Request breath sample • Request blood sample

Sample Size and Statistical Power

Selected Sites. NHTSA is working with three Level 1 trauma centers located in Charlotte, North Carolina, Jacksonville, Florida, and Miami, Florida. They were selected by NHTSA because they each have qualified research staff and high numbers of patients with injuries resulting from motor vehicle crashes. Importantly, these centers are all located in temperate climates with "normal driving conditions." This allows ideal conditions for data collection, as the research can continue year-round and the study will not be hampered by severe weather on a regular basis. These trauma centers offer NHTSA the best opportunity to gather the necessary 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 for the risk estimates for drugs, including alcohol. No individual data will be identifiable.

Sample Size for BAC. Hsieh (1989)[13] presents a method for computing sample sizes for unconditional logistic regression where the independent variable and covariates are continuous. A copy of the Hsieh paper is appended to this submission. His tables show sample sizes for powers of .70-.95 at alpha=.05 (one-tailed). These tables are univariate and hence are based on the crude-odds ratios, but Hsieh provides a formula that allows an adjustment for multiple covariates based on the multiple R^2 for the relationship between the covariates considered to be the independent variable (e.g., alcohol and drug status) and the other covariates. We could not find a published nomogram or table for computing power for a logistic regression model that matches the proposed design (i.e., 1:2 matched design involving multiple covariates where the covariates include both binary and continuous measures).

For this study's power analysis, a value of $R^2 = .04$ was assumed based on the Virginia Beach crash risk study results.[2] In the case of BAC and using the results obtained in Virginia Beach, one standard deviation above the mean represents a BAC of .018. These tables are applicable to assessing models where all the covariates are continuous (e.g., BAC) but would not be strictly applicable to binary covariates or a matched design. Hsieh refers to a paper by Dupont[14] based on the McNemar test and to Fleiss[15] for the case where the risk is dichotomous. Because BAC is continuous, the Hsieh tables are applicable in the present study to BAC.

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[13] Hsieh, F.Y. (1989). Sample Size Tables for Logistic Regression. *Statistics in Medicine, 8*, 795–802.
[14] Dupont, W.D. (1988). Power Calculations for Matched Case-Control Studies. *Biometrics*, *44*(4), 1157–1168. http://doi.org/10.2307/2531743
[15] Fleiss, J. (1981). *Statistical Methods for Rates and Proportions*. New York: Wiley.

Tables 1 and 2 show the estimated total combined sample sizes needed to achieve a power of .80 using a one-tailed alpha=.05 and range of effect sizes (odds ratios) for various prevalence rates for BAC. The multiple R^2 variance inflation factor was set at .04 based on the Virginia Beach study.

Table 1. BAC: Total sample size (crash + controls) needed to detect various increases in risk (crude odds ratio) at alpha ≤ .05 and power=.80. The odds ratios correspond to a one standard deviation from the mean value of the covariate (BAC).

Prevalence*	Odds Ratio					
	1.1	1.2	1.3	1.4	1.5	2.0
4%	18,371	**5,012**	2,414	1,464	1,006	344
8%	9,873	2,699	1,304	794	548	196
12%	7,041	1,928	934	571	396	146
16%	5,624	1,542	749	459	320	121
20%	4,774	1,311	638	392	274	106

*Prevalence of BAC in control sample. ^The highlighted cell is the total sample size required to reliably detect a 20% increase in relative risk (1.2 odds ratio) for alcohol with a 4.0% prevalence rate in the control sample. The proposed sample size greatly exceeds this number and the relative risk for alcohol is known to be substantially higher than the 1.2 odds ratio.

Table 2. BAC: Total sample size (crash + controls) needed to adjust the estimates in Table 1 for the presence of multiple covariates (adjusted odds ratios)

Prevalence*	Odds Ratio					
	1.1	1.2	1.3	1.4	1.5	2.0
4%	19,13 6	**5,220**	2,515	1,525	1,048	358
8%	10,28 4	2,811	1,358	827	571	204
12%	7,333	2,008	973	595	413	152
16%	5,858	1,613	780	478	333	126
20%	4,973	1,365	665	408	285	110

*Prevalence of BAC in control sample. ^The highlighted cell is the total sample size required to reliably detect a 20% increase in relative risk (1.2 odds ratio) for alcohol with a 4.0% prevalence rate in the control sample. The proposed sample size greatly exceeds this number and the relative risk for alcohol is known to be substantially higher than the 1.2 odds ratio.

The tables above indicate that inclusion of multiple covariates only slightly increases sample size requirements. Much more critical is the prevalence (*P*) of a risk factor in the at-risk population and the assumed odds ratio. The Virginia Beach study found alcohol in 2.9% of the control drivers, and the most recent NRS study found alcohol in 8.3% of weekend nighttime drivers who volunteered for a roadside breath test. Given that this study is focusing only on the most severe crashes, we expect to be conducting more roadside sampling at night when prevalence rates are higher. Therefore, we anticipate the overall alcohol prevalence rates for the control sample will be somewhere between 4.0% - 8.0%. In addition, the expected effect size for BAC based on prior research is very large (greater than 2.0 even at a moderate BAC of .05 g/dL). Given the expected prevalence rates and effect size for alcohol, the sample size of 7,500 (2,500 crash and 5,000 controls) proposed in the present study is more than sufficient to study the impacts of alcohol. As demonstrated by the highlighted samples size requirements in Tables 1 and 2, the proposed combined sample size will be able to reliably detect a 20% increase in the relative risk associated alcohol (1.2 odds ratio). In fact, a much smaller sample would be sufficient if the study only investigated the effects alcohol, but as discussed later, the large sample size of this study is required to explore a variety of other drugs at lower prevalence rates and expected effect sizes.

It should be noted that Tables 1 and 2 are based on a one-tailed alpha. If a two-tailed alpha is adopted, the necessary N to achieve a given power would be substantially increased. Another issue is that the Hsieh tables are based on an unconditional non-matched sampling model. However, Peck, Gebers, Voas and Romano's[16] reanalysis of the Long Beach-Fort Lauderdale study found very little difference between the model fit and precision of unconditional and conditional models applied to the same data. Conditioning on the matched pairs resulted in only a 4% improvement in fit as measured by the Cox-Snell R^2 and produced very similar relative risk curves. The proposed sampling plan is sufficient to achieve a power of .80 because the contemplated effect size for alcohol is known to be large.

Sample Size for Other Drugs. Tables 3 and 4 show the sample size/power analysis for the drug component of the study. Table 3 presents estimated number of crash drivers needed and power estimates for a 1:2 matched design with no covariates other than drug status. These tables are based on Dupont (1988). Table 4 shows the needed sample size (crash drivers only) when covariates are added (e.g. age, gender) using the same Hsieh method for estimating covariate inflation. Again, the addition of covariates has little effect on sample size and statistical power.

[16] Peck, R.C., Gebers, M.A., Voas, R.B., & Romano, E. "Improved Methods for Estimating Relative Crash Risk in a Case Control Study of Blood Alcohol Levels", ICADTS, Seattle, Washington, August 26-30,

It is important to note that Tables 3 and 4 show the required number of crash driver cases excluding controls because they are based on the Dupont paper which presented the data in this manner. The total sample size including controls can be calculated by multiplying the cell numbers by three.

Table 3. Drugs: Number of crash drivers needed to detect given univariate effect sizes for various drugs as significant at P≤.05 and power=.80 (1:2 matched control design with zero covariates)

	Odds Ratio					
Prevalence*	1.1	1.2	1.3	1.4	1.5	2.0
1%	60,000	15,400	7,000	4,040	2,650	725
2%	30,400	7,820	3,570	2,060	1,350	375
3%	20,550	5,300	**2,420**	1,400	920	255
4%	15,640	4,030	1,850	1,070	700	196
5%	12,700	3,280	1,503	870	570	160
6%	10,750	2,780	1,275	740	490	140
7%	9,360	2,420	1,115	650	425	120
8%	8,320	2,160	990	580	380	110
9%	7,520	1,950	900	525	350	100
10%	6,900	1,790	825	480	320	92

*Prevalence of drugs in control sample. ^The highlighted cell is the crash driver sample size required to reliably detect a 30% increase in relative risk (1.3 odds ratio) for a drug (or class of drugs) with a 3.0% prevalence rate in the control sample.

Table 4. Drugs: Number of crash drivers needed to detect significant given effect sizes (odds ratio) at P≤.05 and power=.80 (1:2 case control design with multiple covariates)

	Odds Ratio					
Prevalence*	1.1	1.2	1.3	1.4	1.5	2.0
1%	62,500	16,040	7,290	4,230	2,760	755
2%	31,670	8,150	3,720	2,150	1,405	390
3%	21,405	5,520	**2,520**	1,460	958	265
4%	16,290	4,200	1,930	1,115	730	205
5%	13,230	3,415	1,565	905	595	165
6%	11,200	2,895	1,330	770	510	145
7%	9,750	2,520	1,160	675	440	125
8%	8,665	2,250	1,030	605	395	115
9%	7,835	2,030	938	545	365	105
10%	7,190	1,865	860	500	335	95

*Prevalence of drugs in control sample. ^As shown by the highlighted cell, accounting for multiple covariates requires a slightly higher sample size (crash driver N = 2,520) than that proposed to reliably detect a 30% increase in relative risk (1.3 odds ratio) for a drug (or class of drugs) with a 3.0% prevalence rate in the control sample. The proposed sample size will be sufficient if the prevalence rate and/or effect size is just marginally higher for a given drug or class of drugs.

In the Virginia Beach study, few individual drugs had a prevalence rate high enough for statistical analysis. As such, classes of drugs were analyzed in most cases (except for marijuana). As shown in Table 5, the prevalence of a given class of drugs was

relatively small for most classes and varied by whether an oral fluid or blood sample was provided. The exact prevalence of the various drugs of interest is unknown for the current study sites but having three locations will allow for the collection of a larger and more representative sample. The power estimates in Tables 3 and 4 suggest the proposed sample of 2,500 injured drivers will be sufficient to reliably detect an increased risk of being severely injured in a crash at an odds ratio of 1.3 (or just slightly higher when accounting for multiple covariates) for drug classes with a population prevalence rate of 3% or higher. Given the higher prevalence rate for marijuana, the study should be able to reliably detect an effect at an odds ratio of 1.2 or higher. Overall, the injured driver sample of 2,500 drivers will be sufficient to allow NHTSA to determine if any of the drug classes of most interest have a meaningful impact on being severely injured in a crash.

Table 5. VA Beach Crash Risk Study Prevalence of Drug Classes

	Oral Fluid			Blood	
Drug Class	Crash	Control		Crash	Control
Marijuana (THC)	7.6%	6.1%		5.6%	6.7%
Antidepressants	1.4%	1.3%		4.3%	2.5%
Narcotic Analgesics	3.4%	3.0%		1.4%	1.8%
Sedatives	2.9%	2.3%		4.9%	3.8%
Stimulants	3.8%	3.6%		5.1%	3.3%
Other	0.7%	0.5%		1.5%	0.7%

Statistical Analysis Plan

The primary objective of this project is to examine the risk of serious or fatal injury in motor vehicle crashes when alcohol and/or drugs are used by drivers. The relationship between BAC levels, drug status, and injury/fatality crash risk will be evaluated through a series of conditional logistic regression models similar to the design used in the Virginia Beach and Long Beach-Fort Lauderdale studies.[2,5] Two non-crash drivers (controls) will be matched to each injured crash driver. The control participants will be selected by identifying drivers who are driving one week later at approximately the same location, direction of travel, and hour of day as each matching crash driver. Hence, it is a 1:2 conditional logistic regression design in which the controls represent a similar exposure and at-risk driving population as the crash drivers. The use of two controls per each crash case provides increased statistical power. Both univariate and multiple logistic analyses will be conducted. The univariate models will provide estimates of the “crude” odds ratio for BAC and each drug’s relationship to crash rate separately. The multiple logistic regressions provide estimates (odds ratio) of each relationship adjusted for covariates (e.g., age, sex).

The process will begin with an analysis of BAC with and without demographic covariates. This analysis will result in a curve showing how risk of being severely or fatally injured in a crash relates to BAC. These analyses will allow for comparisons with the risk curves obtained in the Fort Lauderdale-Long Beach and Virginia Beach studies. One issue that needs to be addressed concerns the method used to account for non-

linearity of the relationship between BAC and crash risk. One of the aforementioned studies used a cubic polynomial model while the other used a fractional polynomial model. In a sense, they are different approaches to the same objective and the shape of the curves produced in the two studies were very similar. The current study will explore both alternatives. The fact that the present study is limited to injury crashes and severely injured drivers means that this study may produce a different risk curve than the prior studies.

After the above analyses are complete, the second phase of the analyses will address the role of drug impairment and drug by BAC interactions. This objective is far more complex than that of alcohol alone due to the large number of drugs, the more complex pharmacokinetics, and likely low prevalence rates. Placing drugs in broader pharmacological categories, such as those used in the Virginia Beach categories, will be explored in the current study.

As with BAC, three sets of analyses will be conducted. The first will be a univariate logistic regression of the crude odds ratios between each drug class and risk of severe injury. The second analysis will add covariates (e.g., age, sex) to produce odds ratios adjusted for differences between the crash and control groups on potentially confounding covariates. The third set will include both drug class and BAC along with BAC by drug interaction terms.

The analysis involving drugs will not require the use of polynomials to adjust for any non-linearity in the logits because most of the drug variables will be binary (0 = negative; 1 = positive test) due to sample size limitations. In some instance (e.g. THC), sample sizes may be sufficient for evaluating THC as a three-level ordinal variable using ordinal regression techniques. The three THC levels may also be treated as categorical variables through use of dummy codes. These decisions cannot be definitively made until the data becomes available for inspection.

In addition to drug by BAC interactions, analyses will focus on selected drug by driver and crash characteristic interactions (e.g., drug x gender, drug x age, and drug x time of crash). One problem with including interaction terms is that they result in smaller counts within each data cell than the main effect term and less statistical power for detecting a given effect size. This limitation may preclude including anything beyond two-way interaction terms in the model.

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

The potential respondent universe is comprised of all drivers in the trauma centers' catchment areas. From this universe, participants will include seriously injured drivers who are treated in a trauma center after a crash. Participants will also include fatally injured drivers who die before or during treatment within the study catchment area. This study will employ a case-control design that matches two drivers not involved in a crash (controls) to every crash-involved driver. Control drivers will be selected at or near the location of the crash where a driver was seriously or fatally injured. Researchers

will match control drivers based on crash day of the week, crash time of day, and crash direction of travel. The participant groups being sought include a minimum of 2,500 crash-involved drivers and at least 5,000 control drivers. Each participant will only respond to the data collection request a single time during the study period.

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

This study will employ a case-control design that involves comparing two sampled control drivers not involved in a crash for every severely/fatally injured driver. The data collection procedures will vary by participant group given that the nature of the circumstances under which sampling will take place are different. A description of the data collection protocol is provided below.

Crash-Involved Drivers

The trauma centers and medical examiners will provide de-identified samples and information on seriously or fatally injured drivers of motor vehicles (n = 2,500) in the study catchment area. Any driver, regardless of crash fault, will be included in the study. The general participant flow for crash-involved drivers is as follows:

- Crash occurs / EMS on scene
- Triage by EMS or at trauma center
- Seriously injured driver sent to trauma center; fatally injured sent to coroner
- Trauma center or medical examiner provides de-identified blood sample collected during normal procedures

In all cases, blood samples will be obtained as soon as possible after the crash under a waiver of consent which was 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.[17] 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*

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

- *whenever appropriate, the subjects will be provided with additional pertinent information after participation.*

The trauma centers are gathering demographic, treatment, and crash location information under a waiver of HIPAA authorization as granted by the reviewing IRBs – Advarra[18] and University of Florida. The centers will provide the de-identified blood. The results from the laboratory toxicology testing will be stored, with no subject-identifiable information, and only by a study ID in the study database. Results will only be reported at the group level. HHS and Department of Transportation regulations provide for such waivers as detailed below, and for which the two IRBs have approved this research.[19]

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.*

All blood samples will be stored by a study tube number – there will be no information identifying the driver - and sent to the 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. 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 hospitals, and the toxicology results will never be included in participant medical records.

Throughout the study, protocols have been designed to prevent any linkage to an individual participant. As such, law enforcement and legal teams will not be able to link results to a given individual, even with a subpoena. In addition, there will be no records of exactly who had access to or handled the various samples at any given time. As such, no

[18] Previously known as Chesapeake IRB.
[19] https://www.hhs.gov/hipaa/for-professionals/privacy/guidance/research/index.html

individual's toxicology results would be admissible in court given the lack of linkage (that is, the "chain of custody" has been broken).

Control Drivers

Control drivers will be recruited from free-flowing traffic at or near the location of the crash where a driver was seriously or fatally injured. Researchers will select locations for data collection of control drivers that match crash drivers by crash day of the week, crash time of day and, crash direction of travel. Two control drivers for each crash-involved driver (n = 5,000) will be recruited one to two weeks after the crash.

Control drivers will be administered the survey, and will be asked to provide breath and blood samples. All of this data will be anonymous as no identifying information on control drivers is being collected. Participant flow for control drivers is as follows:

- Recruit driver from free-flowing traffic and request consent
- Survey driver
- Request breath sample
- Request blood sample

If the data collector believes that the driver is impaired, for any reason, the study's protocol includes several strategies to get the person home safely, with no involvement of law enforcement and no cost to the driver.

Local law enforcement officers, or retired officers, will be used to help the researchers in ensuring the safety of the drivers and research team. Officers will not be involved in interviewing drivers or collecting data.

B.3. Describe methods to maximize response rates.

For the collection of the control driver data, NHTSA anticipates approaching an estimated 9,000 drivers at roadside with approximately 5,000 consenting to participate. This estimate is based on NHTSA's experience in past studies with recruiting drivers from the roadway and asking for biological samples, including the National Roadside Study[9] and the Virginia Beach study[2] as shown in the highlighted cells in the tables below.

Table 6. Participating Drivers in All Five National Roadside Surveys

				2007			2013		
	1973	1986	1996	Daytime	Nighttime	Total	Daytime	Nighttime	Total
Signaled to enter location	--	3,260	6,480	3,516	9,553	13,069	3,385	10,782	14,167
Did not enter location[a]	--	217	182	933	1,016	1,949	711	2,134	2,845
Stopped and entered location	--	--	--	2,583	8,537	11,120	2,674	8,648	11,322
Eligible	3,698	3,043	6,298	2,525	8,384	10,909	2,617	8,483	11,100
Entered location and interviewed	3,353 90.7%	2,971 97.6%	6,045 96.0%	2,174 86.1%[b]	6,920 82.5%[b]	9,094 83.4%[b]	2,174 83.1%[b]	6,630 78.2%[b]	8,804 79.3%[b]
Valid breath sample	3,192 86.3%	2,850 93.7%	6,028 95.7%	2,254 89.3%[b]	7,159 85.4%[b]	9,413 86.3%[b]	2,361 90.2%[b]	7,094 83.6%[b]	9,455 85.2%[b]
Oral fluid sample	--	--	--	1,850 73.3%[b]	5,869 70.0%[b]	7,719 70.7%[b]	1,986 75.9%[b]	5,895 69.5%[b]	7,881 71.0%[b]
Blood sample	--	--	--	N/A[c]	3,276 39.1%[b]	N/A[c]	**1,263 48.3%[b]**	**3,423 40.4%[b]**	**4,686 42.2%[b]**
AUD and/or drug questionnaire	--	--	--	1,889 75.2%[b]	5,983 71.4%[b]	7,882 72.2%[b]	1,848 70.6%[b]	5,592 65.9%[b]	7,440 67.0%[b]
Passenger questionnaire	--	--	--	220 8.7%[b]	1,393 16.6%[b]	1,613 14.8%[b]	Not available at time of publication		

[a] When this number was not available (i.e., for six locations and 21 sessions), researchers estimated it based on the type of police involvement at the location. [b] Percentage of eligible drivers. [c] N/A (not applicable) because blood samples were not collected at daytime sessions.
Note: Reprinted from Kelley-Baker, T., Berning, A., Ramirez, A., Lacey, J. H., Carr, K., Waehrer, G., Compton, R. (2017, May). *2013-2014 National Roadside Study of alcohol and drug use by drivers: Drug results* (Report No. DOT HS 812 411). Washington, DC: National Highway Traffic Safety Administration.

Table 7. Virginia Beach Crash Risk: Number of Oral Fluid and/or Blood Samples

	Crash-Involved Drivers	Control Drivers
Total provided oral fluid and/or blood sample	3,196	**6,935**
(percentage of eligible drivers)	(82.2%)	(93.8%)
Provided oral fluid sample (not blood)	1,852	2,881
Provided blood sample (not oral fluid)	25	**16**
Provided oral fluid *and* blood samples	1,319	**4,038**
Perfect oral fluid-based matches (1:2)	3,095	6,190
Perfect blood-based matches (1:2)	588	1,176

Note: Reprinted from Lacey, J. H., Kelley-Baker, T., Berning, A., Romano, E., Ramirez, A., Yao, J., ,… & Compton, R. (2016, December). Drug and alcohol crash risk: A case-control study (Report No. DOT HS 812 355). Washington, DC: National Highway Traffic Safety Administration.

This study's protocols for control driver recruitment will be similar to those for NHTSA's National Roadside Survey efforts. The Government Accountability's Office review of that study's protocols,[20] it stated that the methodology "followed Office of Management and Budget (OMB) standards and guidelines for survey principles related to the protection of privacy. Further, NHTSA's protocols are designed to ensure that drivers understand that participation in the survey is voluntary and anonymous, and, midway through the 2013-2014 survey, NHTSA changed several survey protocols to help drivers understand that they have the choice of whether to participate." Similar to those protocols, this study will use highly-trained researchers, traffic signs placed ahead of the research area noting a "paid survey ahead," and research vans marked with the trauma center's logos or other conspicuous markings. We are maximizing response rates by offering financial incentives to drivers for participation. We will pay $5 for responding to survey questions and providing a breath sample, and another $50 for a blood sample. NHTSA's experience with the Virginia Beach study and other roadside data collection efforts has shown that this level of incentive is appropriate to successfully recruit participants, allowing for the needed sample size and to increase the representativeness of the sample. Additionally, the researchers will provide assurances of anonymity in the informed consent process. Drivers will be assured that no identifying information will be collected, that no individual's data will be identifiable for reports of the study's findings, and that no driver's data will be shared with law enforcement, prosecutors, driver licensing officials, or other regulatory authority.

Regarding the crash-involved drivers, trauma centers routinely collect fluid samples for every patient for which 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.[21] Even if these criteria are not met, the treating professional can use his/her judgment to activate an alert if they suspect a serious injury may have occurred but 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 for every injured driver that has a trauma alert activated. This process provides the best opportunity to gather information on the universe of seriously injured drivers in a given area in as quick a manner as possible to reduce the overall time needed for data collection.

For fatally injured drivers, each site's medical examiners will collect samples during the routine post-mortem examination. Blood samples are routinely gathered for the medical examiner's own testing purposes and residual blood is available for research.

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[20] GAO-18-328R National Roadside Survey Methodology (March 12, 2018)

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

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

We will pilot test all protocols at each trauma center, and for control data collection at each site. We do not anticipate substantive changes to the case-control methodology outlined in this document.

NHTSA has experience obtaining sensitive data, including biological samples from drivers at roadside, 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, including the Long Beach and Fort Lauderdale crash risk study in the 1990s. 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 needed sample size with the least amount of inconvenience and burden to the general public.

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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