Background – A major problem in assessing the impact of drugs on driving is the fact that the variables being measured across studies vary significantly. In studies being reported in a growing global literature, the basic parameters being assessed, the analytical techniques being used, and the drugs being testing for are simply not comparable due to a lack of standardization in the field.

In June 2005, the International Council on Alcohol, Drugs, and Traffic Safety’s [ICADTS] Working Group on “Illegal Drugs and Driving” recognized that a set of standards or guidelines for drugged driving research was sorely needed and recommended that a consensus meeting of international researchers should be held to develop standards as a basis for future research.

In September 2006, after more than a year of planning and organization, the consensus meeting was held at the Tufts University European Center in Talloires, France. The international experts in attendance represented nine countries and three continents. The meeting was co-sponsored by the National Institute on Drug Abuse, The European Commission, The European Monitoring Centre for Drugs & Drug Addiction, The International Council on Alcohol, Drugs, and Traffic Safety, The International Association of Forensic Toxicologists, and the French Society of Analytical Toxicologists. The goal of the meeting was to develop a set of standards for “Drugged Driving” research to insure and improve the comparability of data globally.

The product that follows is a set of draft “standards” [Behavioral, Epidemiological, and Toxicology] integrating the discussions and recommendations posed throughout the proceedings of the Talloires meeting. These “standards” were developed utilizing a modified Delphi Method and the draft document is now being posted for a period of 45 days on the ICADTS and TIAFT websites for review and comment by the greater drug-impaired driving research community. It is anticipated that the final version of the Standards Document will be available for distribution at the joint TIAFT/ICADTS meeting in August 2007 in Seattle.

The “Drugged Driving Research” Recommendations are contained in three separate Sections:

Behavioral [32 Recommendations]
Epidemiological [40 Recommendations]
Toxicology [65 Recommendations]

When writing your comments and suggestions, please reference the Section and Specific Recommendation you are referring to. This will facilitate the review of your recommendation/s for possible inclusion in the final document.

Please submit all comments and suggestions to:
TALLOIRES@WALSHGROUP.ORG

Sincerely, J. Michael Walsh
### BEHAVIORAL Section – Recommendations

#### Issue 1 – What Behaviors should be Measured in Drugged Driving Research?

There are 3 core levels of behavior that should be measured to predict crash risks/accidents:

- **Automotive behaviors** – Well-learned skills (e.g.)
  - Tracking, Steering [Road tracking, Critical tracking, compensatory tasks]
  - Vigilance or sustained attention [e.g. Mackworth Clock Test]

- **Control behaviors** – Maintaining distance, passing etc.
  - Motor performance, maneuvers [Reaction time, car following tasks]
  - Divided attention [dual attention tasks]
  - Perception [Time to collision type tasks]

- **Executive planning** – Interactive functions with ongoing traffic
  - Risk taking, impulsivity [e.g. Stop Signal, Iowa gambling tasks]
  - Information processing, Attention [Choice reaction-time, selective or focused attention tasks]
  - Cognition, Judgment – [e.g. Tower of London task]

<table>
<thead>
<tr>
<th><strong>Issue 1 Recommendations</strong></th>
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<tbody>
<tr>
<td><strong>Recommendation 1</strong> – Researchers should use tests that have been validated to be sensitive to drug effects on driver performance, and to the extent possible, have demonstrated predictive validity of driving impairment. However, new behavioral tests that appear promising may be included along with other well-validated tasks.</td>
</tr>
<tr>
<td><strong>Recommendation 2</strong> – Alcohol effects on performance can serve as a standard reference to quantify impairment for many other drugs.</td>
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<tr>
<td><strong>Recommendation 3</strong> – Performance batteries should include a sustained attention task in order to assess drug-vigilance interactions as a function of time working on the task. The duration of the attention task will depend on the half-life of the drug being studied.</td>
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<tr>
<td><strong>Recommendation 4</strong> – A major goal of future research should be the development of specific criteria defining fitness to drive.</td>
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<tr>
<td><strong>Recommendation 5</strong> – Further research to develop a standardized battery of tests is encouraged. Environmental conditions [especially daytime and night-time] should be considered when relevant.</td>
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<tr>
<td><strong>Recommendation 6</strong> – Research to validate new handheld devices being developed for real-time [e.g. road side, ambulatory] testing is also strongly encouraged</td>
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#### Issue 2 – How Many Subjects are Needed in Drugged Driving Studies?

The number of subjects needed to determine the behavioral effects of drugs will depend on the design of the study and the parameters to be studied.

<table>
<thead>
<tr>
<th><strong>Issue 2 Recommendations</strong></th>
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<tbody>
<tr>
<td><strong>Recommendation 7</strong> – Investigators should clearly describe the study population and all subject selection criteria.</td>
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<tr>
<td><strong>Recommendation 8</strong> – A power analysis is needed to determine the required number of subjects. This will be a factor of the sensitivity of the test and the experimental study design.</td>
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<tr>
<td><strong>Recommendation 9</strong> – The demographics of the subject population should be representative of the target population.</td>
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<tr>
<td><strong>Recommendation 10</strong> – It is important to know the current and past drug-use history of all test subjects.</td>
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<tr>
<td><strong>Recommendation 11</strong> – Ideally, medicinal drug studies would be conducted in patient populations. However, healthy volunteer populations can be acceptable as well, unless it is evident that drug effects in this group differ from those in patients.</td>
</tr>
</tbody>
</table>
**Recommendation 12** – Studies involving illicit drugs should be limited to subjects who are current/previous users, and are healthy enough to participate. Those applicants who have medical risks should not be included.

**Recommendation 13** – In the subject selection process, genetic testing should be considered as it can indicate differential sensitivity to drugs.

**Recommendation 14** – Studies in individuals involved in DUI accidents are encouraged, e.g. to identify potential behavioral measures to distinguish crash involved from non-crash involved drivers, or to analyze behavioral factors identified in epidemiological crash analyses.

**Recommendation 15** – Incentives/Compensation to subjects for participation in a research project should be based on the time and inconvenience (not discomfort) involved.

### Issue 3 – What Ethical and Legal Issues should be Considered?

#### Issue 3 Recommendations

**Recommendation 16** – Studies should conform with the legal, and ethical regulations of their respective nations [e.g. Declaration of Helsinki, U.S. Department of Health and Human Services, National Ethics Committees].

**Recommendation 17** – All studies should be designed to minimize the risks to the subjects, the investigators, and the public in general.

### Issue 4 – What “Core” Drugs/Drug Classes should be Included in the Toxicology Test Panel for Behavioral Studies?

A consensus was reached that behavioral studies typically focus on a particular drug of interest, and a number of doses of that drug. Reviewing the last 10 years of drugged driving research, we find that there are six classes of drugs that are most frequently seen in DUI arrests and motor vehicle crash victims: Cannabis, Benzodiazepines & other tranquilizing agents, Opiates, Stimulants [Amphetamine, Cocaine, Methamphetamine, MDMA], Antidepressants, and Antihistamines. Therefore, we believe it is important to test for these drugs in studies designed to examine the behavioral effects of drugs on driving.

#### Issue 4 Recommendations

**Recommendation 18** – In studies designed to assess the impact of drugs on driving, we recommend that the core drug-test panel should include Cannabis, Benzodiazepines & other tranquilizing agents, Opiates, Stimulants [Amphetamine, Cocaine, Methamphetamine, MDMA], Antidepressants, and Antihistamines.

**Recommendation 19** – Studies should also be done with novel drugs. Drugs of interest include: new synthetic drugs in the Opioid class [i.e. Oxycodeone, Hydromorphone, Fentanyls] and novel stimulants [methylphenidate, modafinil]. Additional studies should be conducted to link the behavioral impairment with toxicological and other epidemiological factors where this data as yet does not exist.

**Recommendation 20** – Of particular interest and importance are studies of drug/drug or drug/alcohol combinations because of increased risk associated with these combinations in crash risk studies.

### Issue 5 – What are the Best Specimens to use to Correlate Behavioral Impairment with Drug Levels, and when should these Specimens be Collected?

There is a consensus acknowledging the complex interactions of the drug, the dose, the route of administration, the CNS effects, and the ultimate outcome on behavior [Figure 1].

#### Issue 5 Recommendations

**Recommendation 21** – Blood is the minimum specimen required to determine acute effects of drugs on behavior.

**Recommendation 22** – The behavioral effects of drugs should be related to dose and drug concentration in the brain. Currently, the best available indicator of the drug concentration in the brain is the concentration of the drug in blood. Studies that will look at the correlation between blood concentration and brain activity are encouraged.
**Recommendation 23** – Urine specimens are particularly valuable to document or exclude prior drug consumption.

**Recommendation 24** – Hair specimens may be useful in studies of chronic use.

**Recommendation 25** – It is advisable to take a sufficient number of blood samples to characterize the full pharmacokinetic (PK) profile after a single drug dose.

**Issue 6** – How Long after Drug Administration [time interval] should Performance be Tested?

**Issue 6 Recommendations**

**Recommendation 26** – At a minimum, performance should be assessed at Tmax [when the drug concentration is at a maximum in the blood] to determine the acute effects. Ideally, behavioral assessments should be conducted repeatedly over time to capture and fully characterize the entire PK/Pharmacodynamic (PD) profile including residual or hangover effects.

**Recommendation 27** – It is advisable to always include blood samples with performance testing.

**Issue 7** – Are there Special Considerations researchers should be aware of with regard to Chronic Drug users and Behavior?

Not much research has been conducted on the performance effects of chronic drug use. Specific issues relating to chronic use include: Withdrawal, Chronic Tolerance, Multiple drugs/drug interaction, Steady states, and Long-term (persistent) effects.

**Issue 7 Recommendations**

**Recommendation 28** – In studies designed to assess the chronic use of drugs, performance tests should be repeated during a relevant time period (within-group testing). Ideally, a drug-free baseline measurement should be performed before chronic drug administration. Additionally, a matched control group of non-drug users should be considered (between group testing). Prior drug use should be determined as comprehensively as possible.

**Issue 8** – General Issues Related to the Study Design

**Issue 8 Recommendations**

**Recommendation 29** – It is advisable to include multiple doses in performance studies in order to define dose and concentration – effect relations on behavior.

**Recommendation 30** – Dose ranges employed in experimental studies should preferentially cover the full therapeutic range (medicinal drugs) or reflect real world drug-use patterns (drugs of abuse).

**Recommendation 31** – Placebo controlled and active verum are strongly encouraged

**Recommendation 32** – Performance baselines should be established [i.e. subject trained to plateau levels] prior to study onset in order to eliminate learning effects.
Behaviors to Measure:

- "SKILLS"
- "OTHER"

Traffic Accidents

How to do this?

Sensitivity
Specificity

SUBJECT

Genetics
Experience (drugs, others)
Individual factors

DRUG DOSE

CNS EFFECTS

BLOOD

HAIR

SALIVA

SWEAT

URINE

FIGURE 1
EPIDEMIOLOGICAL Section – Recommendations

Recognizing that the type of research will dictate the required research parameters, our recommendations for epidemiological research are presented in the three following parts which all follow parallel construction:
Part I – Roadside Surveys / Prevalence Studies
Part II – Hospital Studies
Part III – Fatal Crash/Collision Studies

Part I – Roadside Surveys / Prevalence Studies

Issue 1 – Legal/Ethical Issues in Roadside Surveys / Prevalence Studies:
To conduct roadside / prevalence surveys more easily, law enforcement authorities should be willing, funded, legally authorized, and able to participate in them. Prior to the initiation of a study, procedures should be developed to handle obviously impaired drivers encountered while gathering data at roadside surveys.

Issue 1 Recommendations
Recommendation 1 – Contact should be made with relevant authorities (local, regional, and national organizations) to assure compliance with institutional and research requirements and protection of study subjects.
Recommendation 2 – In order to ensure identification but assure anonymity, collected specimens should be identified by a coded identification number only, not a name.
Recommendation 3 – Recording any information that would allow others to trace back and identify the subject should be avoided.
Recommendation 4 – A leaflet describing the purpose of the research (including information on confidentiality and anonymity) should be given to all subjects included in the study.

Issue 2 – What are the Subject and Study Design Issues that should be considered in conducting Roadside Surveys / Prevalence Studies?

Issue 2 Recommendations
Recommendation 5 – A power analysis should be used to ensure that a sufficient number of subjects are included in the study design to be representative of the general population of drivers of motorized vehicles.
Recommendation 6 – In general, subjects should be selected on a random basis recognizing that there may be problems with professional drivers [e.g. taxi, truck drivers, etc.]. A sub sample is possible as long as you clearly state that the results are limited to that subset.
Recommendation 7 – Bias should be avoided in the subject selection process. Refusals can be reduced by ensuring confidentiality and privacy of the data during the research study. Subjects should be provided with precise information regarding: purpose of the study, minimal time required.
Recommendation 8 – A representative sample should be ensured by identifying subjects based on traffic patterns (night, day), timing, location etc. and during the study planning or piloting phases, potential biases should be identified and accounted for in the study design/analysis.
Recommendation 9 – According to each country’s ethical rules, volunteer subjects should receive fair compensation based on the amount of time spent participating in the research (a minimal burden should not result in financial compensation).
**Recommendation 10** – In order to examine possible bias, when an individual refuses to participate in the research project, the researcher should endeavor to get as much objective information as possible on the person who refuses including core demographic data similar to enrolled participating subjects (e.g. gender, age range, etc).

**Recommendation 11** – Refusal rates and characteristics of refusers versus enrolled subjects should be examined. The validity of the study will depend on whether refusal-rates introduce bias.

**Recommendation 12** – The maximal allowable refusal-rate in roadside surveys / prevalence studies will depend upon the purpose of the study and the prevalence of drug use.

**Issue 3 – What are the Core Data Parameters for Roadside Surveys / Prevalence Studies?**

Limitations may depend on costs, laws, and regulations.

*Issue 3 Recommendations*

**Recommendation 13** – At a minimum, data on the following parameters should be gathered:

1. Demographic data including age, sex, level of education, and nationality.
2. Type and age of vehicle.
3. Time and place of the control.
4. Toxicology on the core basic drug groups: Alcohol, cannabis, cocaine, opiates, XTC, amphetamines, and benzodiazepines.

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**Part II – Hospital Studies**

**Issue 4 – Legal/Ethical Issues in Hospital Studies:**

*Issue 4 Recommendations*

**Recommendation 14** – A leaflet describing the purpose of the research (including information on confidentiality and anonymity) should be given to all subjects included in the study.

**Recommendation 15** – Standards for obtaining informed consent in hospitalised injured patients are different from other settings because of the frequent presence of head injuries, shock, intubation, severe intoxication and other medical issues. Therefore, options for obtaining the deferred or surrogate consent should be explored and clarified prior to beginning the study.

**Recommendation 16** – Information obtained for research purposes should be separated from police/medical records.

**Issue 5 – What are the Subject and Study Design Issues that should be considered in conducting Hospital Studies?**

*Issue 5 Recommendations*

**Recommendation 17** – Laws and regulations should be reviewed to determine whether consent is needed to draw a blood sample.

**Recommendation 18** – In the study design, researchers should determine whether to draw blood before or after consent. Pollution, or dilution of blood sample with plasma expanders or drugs should be noted.

**Recommendation 19** – Blood samples should be collected as soon as possible after the accident or injury. The interval between the accident/injury and the time the sample is drawn is a critical element. Time of accident and time samples are collected should be recorded.

**Recommendation 20** – Patients who are intoxicated are more likely to be transported to the hospital. When transferred to the emergency room, intoxicated patients are more likely to be admitted at the hospital. This may introduce bias in the sample. To the extent possible, other sources of data should be examined to try to determine the extent of this bias.
**Recommendation 21** – If attempting to link roadside/prevalence studies and hospital studies, researchers should pay attention and try to screen for the same drug panels in the same biological fluid using the same lab techniques in both studies.

**Recommendation 22** – Researchers should obtain information regarding subjects’ pre-hospital medication during the transfer of the patient from the place of the crash to the hospital.

**Recommendation 23** – If possible, dedicated research staff responsible for data coordination should be present in the hospital 24hrs/day, 7 days/week.

**Recommendation 24** – Studies should try to cover more than one hospital, as those limited to a single hospital may not see a representative sample of all crash drivers, and other motor vehicle crash victims.

**Recommendation 25** – In the study design, researchers should consider the problems associated with the testing of live drivers; lack of facilities to conduct screenings; and lack of collaboration with police.

**Recommendation 26** – A power analysis should be used to ensure that a sufficient number of hospital study subjects are included in the study design to be representative of the general population of drivers of motorized vehicles.

**Recommendation 27** – Bias should be avoided in the selection process. The enrolment of subjects should be without any consideration of age, gender, or race.

**Recommendation 28** – Compensation for hospital study subjects should be avoided unless long questionnaires and interviews are required and this should be done in accordance with each country’s ethical rules.

**Recommendation 29** – In order to examine possible bias, when an individual refuses to participate in the hospital research project, the researcher should endeavor to get as much objective information as possible on the person who refuses including core demographic data similar to enrolled participating subjects (e.g. gender, age range, etc).

**Recommendation 30** – Hospital study refusal rates should to be examined. The validity of the study will depend on whether refusal-rates introduce bias.

**Recommendation 31** – The maximal allowable refusal-rate in hospital studies will depend upon the purpose of the study and the prevalence of drug use.

---

**Issue 6 – What are the Core Data Parameters for Hospital Studies?**

Limitations may depend on costs, laws, and regulations.

**Issue 6 Recommendations**

**Recommendation 32** – At a minimum, data on the following parameters should be gathered:

1. Time of crash.
2. Time the biological sample was taken [blood is the preferred specimen].
3. Toxicology on the core basic drug groups: Alcohol, cannabis, cocaine, opiates, XTC, amphetamines, and benzodiazepines.

**Recommendation 33** – In addition to the core substances (see Recommendation 32), the scope of the drug panel could be expanded to include other drugs based on the consumption patterns of the country and region(s) in question.

**Recommendation 34** – Based on the purpose of the study, consent should be obtained to link emergency department toxicology reports with other relevant databases [e.g. Police report, Trauma registries, pre-hospital ambulance records, criminal records, injuries of other passengers.] Consent may not be needed if data is linked and all identifiers are removed.
### Part III – Fatal Crash/Collision Studies

**Issue 7 – Legal and Ethical Issues in Fatal Crash/Collision Studies:**

*Issue 7 Recommendations*

**Recommendation 35** – The study design should consider the implications of anonymity and confidentiality not being guaranteed if results of the analysis are positive [Implications for health / life insurance etc.]

**Issue 8 – What are the Subject and Study Design Issues to consider when conducting Fatal Crash/Collision Studies?**

*Issue 8 Recommendation*

**Recommendation 36** – All subjects should be included according to the definition of what constitutes a “fatal crash/collision” in the study design.

**Recommendation 37** – To avoid bias in selection process, prosecutors, coroners and hospital pathologists should be involved in the study to ensure all toxicology and autopsy analyses are completed. Training of all these parties is essential as well as collaboration with the police attending the accident.

**Issue 9 – What are the Core Data Parameters for Fatal Crash/Collision Studies?**

Limitations may depend on costs, laws, and regulations.

*Issue 9 Recommendations*

**Recommendation 38** – At a minimum, data on the following parameters should be gathered:

1. Time of the crash.
2. Time the biological sample was taken [blood is the preferred specimen]
3. Toxicology on the core basic drug groups: Alcohol, cannabis, cocaine, opiates, XTC, amphetamines, and benzodiazepines.

**Recommendation 39** – In addition to the core substances (see Recommendation 38), the scope of the drug panel could be expanded to include other drugs based on the consumption patterns of the country and region(s) in question.

**Recommendation 40** – Based on the purpose of the study, consent should be obtained to link toxicology results with other relevant databases [e.g. Police report, Trauma registries, pre-hospital ambulance records, criminal records, injuries of other passengers.]
TOXICOLOGY Section – Recommendations

Recommendations 1 – 15 are specific to Epidemiological Studies
Recommendations 16 – 18 are specific to Checkpoint/Survey Research
Recommendations 19 – 20 are specific to Suspected Impaired Driving Research
Recommendations 21 – 24 are specific to Injury/Trauma Research
Recommendations 25 – 30 are specific to Fatal Injury Research
Recommendations 31 – 66 are General

Issue 1 – What are the Best Specimens to Collect for Epidemiological Studies?

Issue 1 Recommendations

Recommendation 1 – Whole blood is always preferable for interpreting potential drug effects.

Recommendation 2 – In studies designed to assess the prevalence of drug use in drivers and/or the risk of driving performance impairment then the broadest spectrum of licit and illicit drugs should be monitored. It is understood that there are financial consequences to this recommendation and both cost and sample volumes may be limiting factors. However, we strongly recommend that the most impairing and most prevalent drugs in each jurisdiction, county, state or country should be included to the maximum extent practicable.

Recommendation 3 – On-site oral fluid and/or urine tests evaluate a narrow spectrum of drugs at varying sensitivities that may limit drug detectability and each matrix may require analysis of different specific metabolites.

Issue 2 – Specimen Collection

Issue 2 Recommendations

Recommendation 4 – The time interval between driving and specimen collection should be taken into account in the interpretation of test results. Specimen collection should be as soon as possible [preferably within 3 hours] and the time of collection and time between stop and collection recorded.

Recommendation 5 – Ensure that blood is drawn from the opposite arm than any intravenous line to avoid contamination and dilution.

Recommendation 6 – It is suggested that cutoff concentrations be at least as low as the lower end of the therapeutic range.

Recommendation 7 – After collection, specimen should be refrigerated as soon as possible. Analyte stability should be considered with regard to storage and shipment of specimens.

Issue 3 – Recommended Analytes Tested & Maximum Cutoffs in Whole Blood

Issue 3 Recommendations

Recommendation 8 – Alcohol (cutoff, 0.1 g/L)

Recommendation 9 – Opioids: Morphine (cutoff 10 ng/mL), codeine (cutoff 10 ng/mL), 6-acetylmorphine (cutoff 10 ng/mL), methadone (cutoff 10 ng/mL), tramadol (cutoff 20 ng/mL).

Recommendation 10 – Cocaine: Cocaine (cutoff 10 ng/mL) and metabolites (benzoylcegonine 50 ng/mL; cocaethylene 10 ng/mL, ecgonine methyl ester 10 ng/mL).

Recommendation 11 – Cannabinoids: Δ9-tetrahydrocannabinol (THC; 1 ng/mL), 11-nor-9-carboxy-THC (cutoff 5 ng/mL), 11-OH-THC (cutoff 1 ng/mL).

Recommendation 12 – Benzodiazepines: Diazepam (cutoff 20 ng/mL), oxazepam (cutoff 50 ng/mL), temazepam (cutoff 50 ng/mL), alprazolam (cutoff 10 ng/mL), clonazepam (cutoff 10 ng/mL), nordiazepam (cutoff 20 ng/mL), lorazepam (cutoff 10 ng/mL), and midazolam (cutoff 20 ng/mL).
**Recommendation 13** – Other hypnotics: Zolpidem (cutoff 20 ng/mL), zopiclone (cutoff 20 ng/mL), diphenhydramine (cutoff 25 ng/mL), and doxylamine (cutoff 25 ng/mL).

**Recommendation 14** – Sedating antidepressants: Amitriptyline (cutoff 25 ng/mL), nortriptyline (cutoff 25 ng/mL), doxepin (cutoff 25 ng/mL), imipramine (cutoff 25 ng/mL), desipramine (cutoff 25 ng/mL), trimipramine (cutoff 25 ng/mL), dothiepin (cutoff 25 ng/mL), mianserin (cutoff 25 ng/mL), and trazodone (cutoff 10 ng/mL).

**Recommendation 15** – And other medications [e.g. butalbital] (cutoff 100 ng/mL), carisoprodol (cutoff 500 ng/mL), fentanyl (cutoff 1 ng/mL), topiramate (cutoff 1 ng/mL), mirtazapine (cutoff 10 ng/mL), and dextromethorphan (cutoff 20 ng/mL), buprenorphine (cutoff 1 ng/mL), flunitrazepam (cutoff 2 ng/mL) and illicit drugs (e.g., phencyclidine (PCP; 10 ng/mL), LSD (cutoff 0.5 ng/mL), ketamine (cutoff 10 ng/mL), cathinone (cutoff 20 ng/mL), and GHB (cutoff 5000 ng/mL; subject to postmortem production) relevant to the individual country or area.

**Issue 4 – Checkpoint/Survey Research**

<table>
<thead>
<tr>
<th>Specimen Collection and/or Testing Issues</th>
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<tbody>
<tr>
<td><strong>Recommendation 16</strong> – For checkpoints, oral fluid (preferably 1 mL) and if possible, 10 mL whole blood with anticoagulant and fluoride preservative.</td>
</tr>
<tr>
<td><strong>Recommendation 17</strong> – If impairment is suspected based on on-site test results or behavioral observations, conduct collection in accordance with suspected impaired driving.</td>
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<tr>
<td><strong>Recommendation 18</strong> – There should be comprehensive testing of a minimum of 5% of specimens with negative on-site test results.</td>
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**Issue 5 – Suspected Impaired Driving Research**

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<tr>
<th>Issue 5 Recommendations</th>
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<tbody>
<tr>
<td><strong>Recommendation 19</strong> – If possible, 10 mL whole blood (with anticoagulant and fluoride) otherwise urine (preferably 30 mL) or oral fluid (preferably 1 mL), depending upon legal requirements of study.</td>
</tr>
<tr>
<td><strong>Recommendation 20</strong> – Police reports with driving behavior, breath alcohol test results and documentation of interviews, admitted drug use, field impairment tests, medical examinations, and presence of paraphernalia should be collected for research purposes.</td>
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**Issue 6 – Injury/Trauma Hospital Research**

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<th>Issue 6 Recommendations</th>
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<tr>
<td><strong>Recommendation 21</strong> – Whole blood [10 mL] should be collected with anticoagulant and fluoride preservation.</td>
</tr>
<tr>
<td><strong>Recommendation 22</strong> – If possible, additional specimens should be collected: oral fluid and urine.</td>
</tr>
<tr>
<td><strong>Recommendation 23</strong> – Estimated time of crash and the time of specimen collection should be documented.</td>
</tr>
<tr>
<td><strong>Recommendation 24</strong> – Information on emergency services and hospital medications administered, and total blood products, intravenous fluid or artificial blood/synthetic hemoglobin provided should be documented.</td>
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**Issue 7 – Fatal Injury Research**

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<tr>
<td><strong>Recommendation 25</strong> – Peripheral blood [10 mL] with anticoagulant and fluoride preservative should be collected.</td>
</tr>
<tr>
<td><strong>Recommendation 26</strong> – If possible, additional specimens should be collected: urine (preferably 10 mL), vitreous fluid (preferably 1 mL left and right eyes).</td>
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<tr>
<td><strong>Recommendation 27</strong> – Estimated time of crash, time of death and time of autopsy (specimen collection) should be recorded.</td>
</tr>
</tbody>
</table>
**Recommendation 28** – Obtain ante-mortem specimens if available, especially in cases where there is a delay in time of death.

**Recommendation 29** – If possible, information on emergency services and hospital medications administered, and total blood or blood substitute provided.

**Issue 8 – How long should specimens be retained after completion of the study?**

**Issue 8 Recommendation**

**Recommendation 30** – Unless there are statutory limitations, specimens should be kept until issuance of all study reports.

**Issue 9 – What standards should be applied to collection devices?**

**Issue 9 Recommendations**

**Recommendation 31** – Whole blood should be collected in a sterile vacutainer type tube with sodium fluoride and anticoagulant; and an inert stopper/container.

**Recommendation 32** – Oral fluid devices should have some type of indicator that illustrates a sufficient amount of oral fluid has been collected to allow analysis. If possible, collection should occur without the use of stimulating agents.

**Recommendation 33** – Urine collection devices should be inert and not adsorb analytes of interest.

**Recommendation 34** – Manufacturers’ should provide recovery data for all relevant drugs for each lot of devices and attempt to minimize variation between available lots.

**Issue 10 – What are the Minimum Analytes to be Tested and Maximum Cutoff Concentrations in Oral Fluid?**

**Issue 10 Recommendations**

**Recommendation 35** – Alcohol (cutoff, 0.1 g/100mL).

**Recommendation 36** – Opioids: Morphine (cutoff 20 ng/mL), codeine (cutoff 20 ng/mL), 6-acetylmorphine (cutoff 5 ng/mL), methadone [EDDP] (cutoff 20 ng/mL), tramadol (cutoff 20 ng/mL).

**Recommendation 37** – Cocaine: Cocaine and metabolites-benzoylcegonine (cutoff 10 ng/mL).

**Recommendation 38** – Amphetamines: Amphetamine (cutoff 20 ng/mL), methamphetamine (cutoff 20 ng/mL), MDMA (cutoff 20 ng/mL), MDA (cutoff 20 ng/mL), MDEA (cutoff 20 ng/mL).

**Recommendation 39** – Cannabinoids: ∆9-tetrahydrocannabinol (THC; 2 ng/mL).

**Recommendation 40** – Benzodiazepines: Appropriate cutoff concentrations in oral fluid are yet to be established, but are likely to be much lower than blood concentrations: diazepam, oxazepam, temazepam, alprazolam, clonazepam, nordiazepam, chlordiazepoxide, lorazepam, and midazolam.

**Recommendation 41** – Other hypnotics: Appropriate cutoff concentrations in oral fluid are yet established: zolpidem, zopiclone, diphenhydramine, and doxylamine.

**Recommendation 42** – Sedating antidepressants: Appropriate cutoff concentrations in oral fluid are yet to be established: amitriptyline, nortriptyline, doxepin, imipramine, desipramine, trimipramine, dothiepin, mianserin, and trazodone.

**Recommendation 43** – And other medications: Appropriate cutoff concentrations in oral fluid are yet to be established. (e.g. butalbital, cocaethylene, carisoprodol, fentanyl, topiramate, nitrazepam, mirtazapine, and dextromethorphan, buprenorphine [norbuprenorphine] and illicit drugs (e.g., phencyclidine (PCP), LSD, ketamine, cathinone and GHB (subject to postmortem production) relevant to the individual country or area.
### Issue 11 – What are Minimum Analytes to be Tested and Maximum Cutoff Concentrations in Urine?

Urine specimens provide a basis for further investigations in blood of relevant drug classes. Detection limits should be as low as analytically feasible. Recommended minimum analytes to be tested in urine:

#### Issue 11 Recommendations

**Recommendation 44** – Alcohol (cutoff, 0.1 g/100mL); report concentration in the matrix used.

**Recommendation 45** – Opioids: Morphine, codeine, 6-acetylmorphine, methadone [EDDP], tramadol. If appropriate for the specific country or area, add oxycodone, hydrocodone, hydromorphone.

**Recommendation 46** – Cocaine: Cocaine and metabolites (benzoylecggonine).

**Recommendation 47** – Amphetamines: Amphetamine, methamphetamine, MDMA, MDA, MDEA.

**Recommendation 48** – Cannabinoids: 11-nor 9-carboxy-THC.

**Recommendation 49** – Benzodiazepines: Diazepam, oxazepam, temazepam, alprazolam, clonazepam, triazolam, nordiazepam, chlordiazepoxide, lorazepam, midazolam, and flunitrazepam.

**Recommendation 50** – Other hypnotics: Zolpidem, zopiclone, diphenhydramine, and doxylamine.

**Recommendation 51** – Sedating antidepressants: Amitryptyline, nortriptyline, doxepin, imipramine, desipramine, trimipramine, dothiepin, mianserin, and trazodone.

**Recommendation 52** – And other medications (e.g. butalbital, cocaethylene, carisoprodal, fentanyl, topiramate, nitrazepam, mirtazapine, and dextromethorphan, buprenorphine [norbuprenorphine] and illicit drugs (e.g., phencyclidine (PCP), LSD, ketamine, cathinone, and GHB (subject to postmortem production) relevant to the individual country or area.

### Issue 12 - Standards Applied for Tests Conducted in the Laboratory (i.e. performance criteria)

#### Issue 12 Recommendations

**Recommendation 53** – Assays should be properly validated. References describing appropriate validation criteria include the SOFT-AAFS Forensic Toxicology Laboratory Guidelines, Peters et al. (Amphetamine method validation), ISO 17025, FDA.

**Recommendation 54** – For research purposes, it is not necessary to perform an immunoassay screening test if tandem mass spectrometry or full scan mass spectrometry is used to identify and quantify analytes of interest.

### Issue 13 – Standards for Tests Conducted at Point of Collection

#### Issue 13 Recommendations

**Recommendation 55** – Manufacturers should provide performance data for sensitivity, specificity, accuracy, and recovery of analytes from the collection device at suggested cutoff concentrations for each lot of devices. The target analyte for each class of drugs and cross-reactivity of closely related compounds should be clearly specified.

**Recommendation 56** – Cutoff concentrations should be specified for undiluted oral fluid.

**Recommendation 57** – Additional specimen volume should be available for confirmatory laboratory-based analysis and allow appropriate chain of custody measures, if necessary.

**Recommendation 58** – The assay should be able to perform acceptably, reproducibly and reliably at cold and hot temperatures and in inclement weather.

**Recommendation 59** – Test results should be available within 5 minutes if possible.
<table>
<thead>
<tr>
<th>Recommendation 60</th>
<th>Preferably, the assay should be convenient, robust and require the least number of reagents and steps possible.</th>
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<tbody>
<tr>
<td>Recommendation 61</td>
<td>Preferably, there will be a small handheld instrument for objective endpoint determination.</td>
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<tr>
<td>Recommendation 62</td>
<td>A minimum of 5% of negative on-site tests should be analyzed by mass spectrometry to evaluate false negative results.</td>
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<td>Recommendation 63</td>
<td>Each device should have a mechanism for assuring accurate device performance.</td>
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<tr>
<td>Recommendation 64</td>
<td>In addition, each analyst should include at least one positive and negative quality control sample for each analyte once each day to verify performance.</td>
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<tr>
<td>Recommendation 65</td>
<td>Minimum drug classes that should be included are cocaine, THC, amphetamines, benzodiazepines, and morphine. Additional analytes or classes to include are carisoprodol, zolpidem, buprenorphine, methadone, and tramadol.</td>
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