PROTOCOL

Identification and characterization of the clinical toxicology of novel psychoactive substances (NPS) by laboratory analysis of biological samples from recreational drug users.

Short title – Identification Of Novel psychoActive substances (IONA)

Chief Investigator

Prof SHL Thomas

Professor of Clinical Pharmacology and Therapeutics, Newcastle University

Consultant Physician, Newcastle Hospitals NHS Foundation Trust (Royal Victoria Infirmary)

Director, National Poisons Information Service (Newcastle) Unit.

Address	Medical Toxicology Centre, Wolfson Building, Newcastle University, Newcastle NE2 4HH
Email	simon.thomas@ncl.ac.uk
Tel	0191 222 8095

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Co-investigators

Newcastle Health Protection Research Unit, Newcastle University

Dr Simon Hill
Dr Mick Dunn
Prof Peter Blain
Dr Christopher M Morris

NIHR Health Protection Research Unit
Medical Toxicology Centre
Wolfson Building
Newcastle University
Newcastle NE2 4HH

Dr Alasdair Blain
Prof Steven Rushton

School of Biology
Newcastle University
Newcastle

NHS Toxicology Laboratories

Dr Nigel Brown

Wansbeck Hospital Toxicology Laboratory
Northumbria Hospitals NHS Foundation Trust. Clinical Chemistry / Toxicology,
Woodhorn Lane, Ashington,
Northumberland NE63 9JJ

Dr Jonathan Berg
Dr Loretta Ford

Toxicology Laboratory, Clinical Biochemistry, City Hospital,
Sandwell and West Birmingham NHS Foundation Trust
Dudley Road, Birmingham, B18 7QH

Dr Alun Hutchings

Cardiff Toxicology Laboratories
The Academic Centre
University Hospital Llandough
Penarth, Vale of Glamorgan, CF64 2XX

National Poisons Information Service

Prof Michael Eddleston
Dr Jonathan Wraight
Dr James Dear

National Poisons Information Service,
Edinburgh Unit, Royal Infirmary of Edinburgh, QMRI, E3.20
47 Little France Cresc
Edinburgh, EH16 4TJ

Dr John Thompson

National Poisons Information Service,
Cardiff Unit, Academic Centre, University Hospital Llandough, Penlan Road, Penarth,
Vale of Glamorgan CF64 2XW

Prof Allister Vale Dr Sally Bradberry	National Poisons Information Service, Birmingham Unit, City Hospital, Birmingham B187QH

NHS Emergency Departments

Dr Stephen Waring	York Teaching Hospitals NHS Foundation Trust, Acute Medical Unit, York Hospital, Wigginton Road, York, YO31 8HE
Dr Simon Hill Dr John Wright	Newcastle Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Queen Victoria Road, Newcastle NE1 4LP
Prof Michael Eddleston Dr Jonathan Wraight	Royal Infirmary of Edinburgh QMRI, E3.20 47 Little France Cresc Edinburgh, EH16 4TJ
Dr Paul Dargan Dr David M Wood	Guy's and St Thomas' NHS Foundation Trust and King's Health Partners Clinical Toxicology, 3rd Floor, Block C, South Wing, St Thomas' Hospital, London SE1 7EH
Prof Allister Vale Dr Sally Bradberry	Sandwell and West Birmingham Hospitals NHS Trust, City Hospital, Birmingham B187QH
Dr John Thompson	University Hospital Llandough, Penlan Road, Penarth, Vale of Glamorgan CF64 2XW
Dr Paul Egdell	Gateshead Hospitals NHS Foundation Trust, Emergency Department, Queen Elizabeth Ave, Gateshead Tyne and Wear NE9 6SX
Dr Johann Grundlingh Barts Health NHS Trust	Emergency Department Acute and Family Division Royal London Hospital Whitechapel London E1 1BB

Dr Anthony Kehoe (To be confirmed)	Emergency Department Derriford Hospital Plymouth PL6 8DH
Further departments and local PIs to be confirmed	

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ABBREVIATIONS

25I-NBOMe	2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl] ethanamine
2-AI,	2-aminoindan
2C-B	2,5-dimethoxy-4-bromophenethylamine
2C-E	2,5-dimethoxy-4-ethylphenethylamine
5-IAI	5-Iodo-2-aminoindane
5-IT	5-(2-Aminopropyl)indole
ACMD	Advisory Council on the Misuse of Drugs
ALT	Alanine transaminase
AM-2201	(1-(5-fluoropentyl)-3-(1-naphthoyl)indole)
AMT	alphamethyltryptamine
APB	aminopropylbenzofuran
APICA	1-Amino-5-phosphonoindan-1-carboxylic acid
AST	Aspartate transaminase
BB-22	1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid 8-quinolinyl ester
BZP	Benzylpiperazine
CK	Creatine kinase
D2PM	Diphenylprolinol
DEWS	Drugs early warning system
DMAR	Dimethylaminorex
DOB	Dimethoxybromoamphetamine
DOM	Dimethoxy-4-methylamphetamine
ECG	Electrocardiograph
EMCDDA	European Monitoring Centre for Drug Dependency and Addiction
FEWS	Forensic Early Warning System
HDU	High dependency unit
HPRU	Health Protection Research Unit
HU	Designation for SCRAs first synthesized by the Hebrew university
IM	Intramuscular
INR	International Normalised ratio
ITU	Intensive therapy unit
IU	International Units
IV	Intravenous
JWH	Designation for SCRAs first synthesized by John W Huffman
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LC-QqTOF	Liquid chromatography-hybrid quadrupole time-of-flight mass spectrometry

LOS	Length of hospital stay
MDA	Methylenedioxyamphetamine
MDAI	Methylenedioxy-2-aminoindane
MDMA	Methelene dioxy methamphetamine
MRC	Medical research Council
MRM	Multiple reaction monitoring
MS	Mass spectrometry
MS/MS	Tandem mass spectrometry
MT-45	1-cyclohexyl-4-(1,2-diphenylethyl)piperazine
NHS	National Health Service
NPIS	National Poisons Information Service
NPS	Novel psychoactive substance
npSAD	National Programme on Substance Abuse Deaths
ONS	Office for National Statistics
PALS	Patient Advice and Liaison Service
PMA	Paramethoxyamphetamine
PLR	Professional legal representative
PMMA	Paramethoxymethamphetamine
PPI	Patient and public involvement
PSS	Poisoning Severity Score
PT	Prothrombin time
RCS4	1-pentyl-3-(4-methoxybenzoyl)indole
SC	Subcutaneous
SCRA	Synthetic cannabinoid receptor agonists
STS	N-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-indole-3-carboxamide
SWATH	Sequential Windowed Acquisition of all THeoretical mass spectra
TCDO	Temporary class drug order
UKPID	UK Poisons Information Database
UR	(1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone
WEDINOS	Welsh Emerging Drugs and Identification of Novel Substances
XLR	5''-fluoro-UR-144
α-PVP	α-Pyrrolidinopentiophenone

SUMMARY

The epidemiology of recreational drug use has changed in recent years as a result of the increasing use of new recreational drugs, sometimes termed Novel Psychoactive Substances (NPS) or 'legal highs.' These are an increasing healthcare challenge, with 73 new substances reported to the Drugs Early Warning system in Europe in 2012 and 81 in 2013. These substances are associated with significant acute toxicity with 56 deaths reported in England and Wales during 2012 and numerous non-fatal episodes of toxicity presenting to hospitals. The effects of chronic exposure are usually unknown, but traditional drugs of misuse that are chemically related to some NPS have been associated with serotonergic neurotoxicity and there is emerging but inconsistent evidence of chronic neurotoxicity in animal studies after exposure to some NPS.

Currently there is no systematic national UK data collection system linking analytically confirmed use of NPS with toxicity. As a result, there may be a delay before clinicians, public health teams, law enforcement and policy makers can define and mitigate the harms associated with specific substances. There are usually no published data available on the pharmacology and toxicity of NPS as they emerge into recreational use, leaving healthcare professionals without evidence to guide patient management in the event of toxicity.

This research will help to address this gap by collating information about NPS implicated in episodes of acute toxicity in the UK. This will include

(1) anonymised aggregated data on clinical enquiries about suspected NPS toxicity collected by the National Poisons Information Service (NPIS)

(2) anonymised aggregated data available on samples positive for NPS from the participating NHS toxicology laboratories that perform extended drug screening on patient samples

(3) Further analysis of anonymised samples collected routinely from patients with acute severe toxicity that are negative on extended screening in participating NHS laboratories, where NPS use is suspected.

(4) Collection and analysis of samples from consenting patients presenting to participating emergency departments with severe toxicity associated with suspected NPS use, with patient consent.

Samples will be subjected to detailed toxicological analysis using state of the art discovery methodology, informed by the latest information on NPS being encountered by clinicians in the UK, as advised by NPIS, and in Europe, as provided by the European Monitoring Centre for Drug Dependency and Addiction (EMCDDA).

The research will identify trends in enquiries and positive laboratory samples relating to NPS, identify NPS involved in episodes of acute toxicity presenting to UK hospitals and link specific substances with reported features of toxicity.

INTRODUCTION

Novel Psychoactive Substances

The epidemiology of recreational drug use has changed substantially in recent years with rapidly increasing use of Novel Psychoactive Substances (NPS) in the UK and internationally. These compounds, sometimes erroneously referred to as 'legal highs' or ‘research chemicals’, are usually chemically similar to traditional drugs of misuse (e.g. amphetamine, MDMA [‘ecstasy’], tryptamines, ketamine, cannabinoids, cocaine or opioids) but with alterations made to the chemical structure so that the new compound is no longer captured by national control of drugs legislation, such as the Misuse of Drugs Act in the UK.[1] Recent examples of NPS include cathinones (e.g. mephedrone[2, 3]), benzofurans (e.g. 5/6 APB[4, 5]), NBOMe compounds,[6-8] tryptamines (e.g. alpha methyltryptamine[9-11]), piperazines (e.g. benzylpiperazine[12, 13]), benzodiazepines (e.g. etizolam[14]), arylcyclohexamines (e.g. methoxetamine[15-17]), synthetic cannabinoid receptor agonists (SCRAs),[18-22] and synthetic opioids (e.g. MT-45)[23, 24]. A more detailed classification of NPS and related drugs of misuse is provided in Appendix 1.

Alterations to the chemical structure of a drug of misuse to produce a NPS can result in a different toxicity profile. As NPS are not subject to any testing prior to distribution and use, some may produce severe and unexpected toxic effects. This may occur as a result of unexpectedly high potency (a low dose is required to produce desired and toxic effects), increased intrinsic toxicity (e.g. toxic effects occur at doses close to those needed to produce the desired effects) or a change in pattern of toxic effects. The All Party Parliamentary Group for Drug Policy Reform have stated that

‘the greatest risk to young people from new psychoactive substances derives from the absence of reliable information about the contents and strength of each new substance and its effects both short and long term’ [25]

NPS present particular challenges to health services because of the rapid emergence of large numbers of different compounds. For example, there were 73 NPS reported in the European Union in 2012, 81 in 2013 and 37 in the first 5 months of 2014, bringing the number monitored

to approximately 400.[26] A further challenge is the lack of available information on their pharmacology or toxicology as there is usually little or no research into these aspects before they are introduced onto the market.

Legal or otherwise, NPS may cause significant acute harms; the Office for National Statistics (ONS) reported 56 deaths in England and Wales in 2012 where an NPS was mentioned on the death certificate following a drug-related death, almost double the figure for 2011.[27] ONS also reported increases in deaths related to specific newer recreational drugs including cathinones (from 6 to 18) and paramethoxyamphetamine (PMA) or paramethoxymethamphetamine (PMMA, from 1 to 20) between 2011 and 2012.[27] There is a lack of available information on indicators of morbidity, such as numbers of hospital attendances or admissions after use of NPS, although enquiries from health professionals to the UK National Poisons Information Service are common and increasing.[28] For most NPS there is almost no available information on the longer term effects of repeated exposure in humans, although severe chronic bladder toxicity may occur after repeated exposure to methoxetamine, as also occurs after exposure to ketamine,a related traditional drug of abuse.[29] Traditional drugs of misuse related to some NPS have been associated with serotonergic neurotoxicity[30] and there is emerging but inconsistent evidence from animal studies of chronic neurotoxicity after exposure to some NPS.[17, 31-40]

This lack of evidence about acute harms and long term effects from use of NPS has been identified as an important evidence gap in a recent Home Office report.[41]A further difficulty is that the chemical composition of products sold may not be known or may not be as advertised to the user[42] and may vary[43] or involve a mixture of compounds,[26] some of which can be illegal.[44, 45]

There is evidence from the UK that legal control of NPS can reduce the frequency of presentations to health services with clinical toxicity associated with that substance. This may be a direct effect of restricting supply, but could also occur because the publicity associated with legal control may better inform clinicians and users about the harms associated with use. For example, for the synthetic cathinone mephedrone (‘M-Cat’), enquiry numbers to the UK NPIS peaked in April 2010 and subsequently declined sharply after legal control; [2] a similar pattern

was observed in one emergency department.[46] These changes are accompanied by evidence of a reduced prevalence of mephedrone use.[41] Reductions in telephone enquiries to the NPIS about cases of toxicity also fell after legal control of methoxetamine.[15] However, legal control of one drug may channel users towards other recreational drugs, including newer NPS, the harms of which may be at least as great as the drug being controlled. As a result, the overall impact of control measures on recreational drug related morbidity and mortality remains uncertain.

Drug control in the UK

In the UK, legal control of drugs of misuse is determined by the Home Office after advice by the Advisory Council on the Misuse of Drugs (ACMD). For control to be recommended under the 1971 Misuse of Drugs Act there must be evidence of harms associated with the drug, such as adverse societal impact or evidence of acute or chronic toxicity. From November 2011, the Misuse of Drugs Act 1971 has been amended to enable the temporary control of an NPS by invoking a temporary class drug order (TCDO). This requires that the substance is not already controlled and is subject to advice from the ACMD that the drug is likely to be misused and misuse is capable of having harmful effects. TCDOs need Parliamentary endorsement within 40 sitting days and last for up to 12 months. This is expected to provide adequate time for the ACMD to provide full, independent and expert advice about the need for permanent control.[a] Mechanisms are therefore needed for rapid collection of information on the potential harms of emerging substances to inform ACMD decisions on TCDOs and permanent control.

The NPIS have published data on the emergence of clinical harm associated with NPS [9, 15] and these data correlate with data from other sources such as the EMCDDA, mortality data published by ONS, published case series and case reports.[47] NPIS data, however, are currently limited by the lack of analytical confirmation of the exact substance(s) involved, relying on information provided by the patient or witnesses. This is suboptimal because preparations sold as one drug may on analysis be found to contain others, delaying the detection and characterization of emerging recreational substances.[45, 48, 49]

[a] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/98006/temporary-class-drug-factsheet.pdf

Research in progress

Various non-systematic and sometimes unfunded research projects are already in place to provide analytical confirmation of NPS in use in the UK. Samples may be taken on an *ad hoc* basis from patients presenting with toxicity when clinicians are aware of laboratories that are able to provide the appropriate analysis. This has provided invaluable information linking features of toxicity with chemical composition, but the data collection is not systematic so sample sizes are limited and often geographically confined. Nationally, most patients present with toxicity without analysis of their samples taking place and this may delay identification of new drug issues. Nevertheless, examples of NPS identified and linked to clinical effects, often by research teams involved in the current project, include mephedrone [50] desoxypipradrol [51], D2PM[52], methoxetamine[15, 17] and 25I NBOMe [7].

Biological samples from patients may also be analysed as part of the forensic analysis of drug-related deaths and this provides essential information which is collated by the National Programme on Substance Abuse Deaths (npSAD). This has reported an increasing number of cases where a NPS has been listed as the cause of death from 10 in 2009 to 68 in 2012.[53] This project, however, is no longer funded and is not collecting information within a meaningful time frame.

The Home Office currently funds a Forensic Early Warning System (FEWS).[54] This is restricted to analysis of powders, such as those seized by customs or police forces. Since inception FEWS has analysed more than 4,500 samples and from these identified 31 novel substances.[55] This provides useful evidence of drugs in circulation but cannot be used to link these substances with particular clinical features of toxicity.

The Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) project was launched in 2013 for the collection and testing of new psychoactive substance (NPS), with dissemination of pragmatic evidence-based harm reduction information via a website.[56] Users are able to send samples of drug they have purchased and also details of clinical features they have experienced from use. Although focused on Wales, the project accepts and analyses drug samples from throughout the UK. From October 2013 to March 2014 the project received and

analyzed 703 samples and in the most recent quarter year notified 12 new substances to the EMCDDA.[57] This project, however, does not routinely collect blood or urine samples from patients experiencing toxicity, although there may be some capacity for this on an *ad hoc* basis. Drug samples provided by users give an indication of the content of substances in circulation but do not necessarily reflect the substances that are actually being consumed.

Research gaps

There is therefore a currently unmet need for a system that provides the opportunity for detailed analysis of blood, urine or other biological samples from users of recreational drugs who experience toxicity irrespective of where they present in the UK. This needs to be simple to access, well publicised to the relevant health professionals and drug user groups, have the appropriate ethical and regulatory approvals in place and be able to link biological exposure with evidence of clinical toxic effects. This would be consistent with the Independent Scientific Committee on Drugs recommendation to

'*Monitor any hospital Accident & Emergency presentations, and clinical assessments, and confirm by urine analysis'*.

A project of this type, termed STRIDA, initiated in Sweden in January 2010, demonstrates the value of this approach. STRIDA received samples from 103 patients in the first year of operation, and the most common NPS groups identified were synthetic cannabinoids (22), substituted cathinones (11) and substituted tryptamines (9) [58]. The STRIDA project has been able to identify emerging NPS and relate exposure to features of toxicity, e.g. 5-IT [59] and MT-45.[24] Other similar projects are operating around the world, but do not provide UK-specific information linking analytically confirmed exposure with toxic effects.

AIMS AND OBJECTIVES

This project will seek to identify NPS that may be involved in toxicity experienced by patients presenting to acute hospitals, especially emergency departments. This will be achieved using routine data collected by UK NPIS poisons centres and NHS Toxicology laboratories together with analytical evidence of exposure to NPS from samples taken either during normal NHS care or, in participating hospitals, for the purposes of the research.

Specific aims of the study are

1. Identify trends in enquiries to the NPIS (telephone and internet) relating to NPS and characterize and monitor the epidemiology of reported exposures
2. Identify trends in the numbers of samples positive for NPS as identified in participating NHS laboratories
3. Develop sophisticated mathematical models for analyzing NPIS and toxicology laboratory data
4. Further develop methods of screening, analysis and quantification for new/emerging NPS in biological samples (urine, oral fluid and blood)
5. Analyse samples from patients with acute severe toxicity relating to NPS to identify responsible agents
6. Link the presence of analytically confirmed NPS exposure with the toxic effects experienced

METHODS

Type of study

The research involves 4 complementary strands, each of which is a non-interventional observational study, using data as follows:

(1) Fully anonymised aggregated clinical data that is routinely collected by the NPIS to identify drugs and products reported to be involved in episodes of toxicity, including temporal and geographic trends.
(2) Fully anonymised aggregated data on findings of extended urine screening performed for drugs of misuse by NHS toxicology laboratories as part of normal clinical practice.
(3) Linked-anonymised residual samples (blood/urine/oral fluid) from those originally sent to NHS toxicology laboratories for toxicology screening as part of that patient's usual clinical care
(4) Research samples (blood/urine/oral fluid) and clinical details, provided with patient consent, from hospital emergency departments participating as research sites.

The study will link the reported history of exposure and/or analytical findings with reported clinical features of acute toxicity.

Participants

The target population is recreational drug users presenting to health services (especially emergency departments) with acute severe toxicity associated with suspected recreational drug use.

Research methods

Study 1. Analysis of NPIS enquiry data

Telephone enquiries to the 4 UK NPIS Units (Newcastle, Birmingham, Cardiff, and Edinburgh) are logged on a common server so that a full national dataset is available to all units in real time. This is necessary to ensure that any NPIS Unit is able to provide further advice about a case that may have previously been handled by a different Unit. This gives the NPIS the capability of putting together aggregated information about enquiries relating to individual substances. There were 1561 telephone enquiries related to 61 drugs of misuse that were being monitored during 2013/14, constituting 3.0% of the 55,000 telephone enquiries handled by the service annually. Of these, 515 related to NPS, including 65, 186 and 168 relating to mephedrone, SCRAs and unspecified 'legal highs' respectively.

NPIS is also able to monitor number of hits to relevant NPS entries on the poisons information database TOXBASE.[60] This gives an indication of how often health professionals seek information about individual substances as a proxy measure of how often these are encountered. During 2013/14 there were over 58,000 TOXBASE accesses relating to the 61 drugs of misuse that were being monitored. This was an increase of 10.3% over the previous year and these substances represent 4.0% of all TOXBASE accesses. These accesses included almost 15,000 to information about NPS.

As part of its public health surveillance function, NPIS currently analyses these data and provides reports on request to official organizations such as the ACMD, DEWS and EMCDDA. Data are also published annually as part of the NPIS annual report. The proposed research will involve more detailed epidemiological analysis using fully anonymised NPIS records. This will include mathematical modeling to study trends and geospatial factors with the intention of developing methods for earlier prediction of public health impact from emerging substances.

Study 1 **Inclusion criteria**	**Exclusion criteria**
• Enquiry involving suspected systemic NPS exposure • Originating from a UK based NHS health professional • Any age	• Non UK enquiries • Enquiries made from educational, public health or governmental sources • Other enquiries not involving a specific patient exposure

Data collected

NPIS is able to provide an anonymised dataset which can be downloaded from its telephone call logging database (the UK Poisons Information Database, UKPID). Anonymised data are also available for accesses to relevant information on TOXBASE. The specific data to be provided for study is listed in the table below

Telephone enquiry records	**TOXBASE access records**
• Date and time of enquiry • Age and sex of drug user • Postcode of enquirer (first 4 digits) • Enquiry source (Hospital, GP, NHS111 etc) • Substance(s) reported and route of administration • Circumstances (accidental, intentional, recreational etc) • Medical history • Clinical features reported • Poisoning severity score[61]	• Date and time of access • Postcode of registered user (first 4 digits)* • Enquiry source (Hospital, GP, NHS111 etc) • Substance accessed *Note that users are registered as whole institutions/departments rather than as individual health professionals

Study 2. Collation of toxicology data provided by participating NHS laboratories

Most NHS laboratories perform limited screening for drugs of misuse, usually involving urine samples, but sometimes oral fluid or occasionally blood. These screens generally cover traditional drugs of misuse and may not identify many NPS. If use of a NPS is suspected, more detailed screening and confirmatory analysis can be sought from a specialist NHS Toxicology lab. The degree of sophistication and detail of the screens varies from service to service. Some offer targeted screening (i.e. are able to screen for compounds with commercially available standards). Some use older gas chromatography – mass spectrometry based systems which may lack information to detect newer drugs. Others have access to newer accurate mass and high resolution MS (time of flight or orbitrap), but may lack the time and/or resources to undertake detailed examination to identify newly emerging substances. The proposed research will involve collation of data on numbers of positive samples for recreational drugs (including NPS, as covered by these screens) for patients with acute toxicity whose samples have been handled in participating specialist toxicology laboratories. These data will be used to study temporal and geospatial trends in positive samples for substances and linked with trends for NPIS enquiry data.

Study 2 **Inclusion criteria**	**Exclusion criteria**
• Person with suspected recreational drug exposure • Sample provided as part of routine clinical care • Any age	• Samples collected for investigation of suspected non-accidental injury • Non UK cases

Data collected

NHS laboratories are able to provide data as supplied to them on the original request form and the following will be provided to the research team for further analysis

- Date and time of sample
- Age and sex of drug user
- Postcode of drug user's NHS registered address (first 4 digits)
- Treating hospital
- Reason for request (routine screening, acute toxicity etc)
- Reported clinical features (note, this is unlikely to be comprehensive)

Study 3. Further analysis of samples already collected as part of clinical care.

This study will use residual linked-anonymised urine/ blood/oral fluid samples taken from people with suspected severe acute toxicity that have already been subject to routine toxicological screening in the NHS specialist toxicology laboratory, with the results of that reported back to the clinical team as normal. These samples will be provided to the HPRU in Newcastle where, using state of the art equipment and methods (full scan MS/MS with SWATH acquisition,[62], further details below) they will be subject to more detailed analysis for detection of NPS that are not detected by extended NHS toxicology screening. Samples included in the research will include:

(a) those found to be negative on an extended drug screen, where toxicity is not associated with the drugs of misuse identified by the screening panel used in the NHS toxicology laboratory.

(b) A selection of samples found to be positive on extended NHS toxicology laboratory drug screening, where the pattern of clinical toxicity is severe or inconsistent with substances identified. This is because the presence of a traditional drug or identified NPS does not exclude co-exposure to other NPS. Such samples can also be used for quality control purposes, ensuring that participating laboratories, including the HPRU, are providing consistent analytical findings.

These samples will be provided to the HPRU together with the clinical information originally provided on the toxicology request form. Samples and data will be provided in linked-anonymised format, with the link to the person's identity being held only in the participating NHS toxicology laboratory. Occasionally, samples of substances taken are also available and these may also be sent with the available clinical samples. Positive analytical results identifying NPS will be passed back to the NHS laboratory providing the sample which will in turn report this back to the clinical team. If further clinical details are required to inform the analysis or interpretation of the result, these would only be sought from the clinical team treating the drug user by staff in the NHS toxicology laboratory. Clinical advice for managing people with suspected drug toxicity is available from the National Poisons Information Service (NPIS) as needed.

Participating NHS labs will obtain local approval as research sites and the research in each will be lead by a principal investigator who will be part of the research team.

Study 3 **Inclusion criteria**	**Exclusion criteria**
• Person with suspected recreational drug exposure • Sample sent from acute NHS hospital • Presence of acute toxicity as reported in request form or sample from an acute hospital site • Sample provided, analysed and reported as part of routine clinical care	• People without evidence of clinical toxicity • Those undergoing routine drug screening as part of drug treatment/rehabilitation • Children and young people <16 y • Samples collected for investigation of suspected non-accidental injury

Obtaining written informed consent for the use of these samples for research is not feasible because this would require the hospital where the drug user is being managed to be a full research site. To obtain wider coverage the study needs to be able to include samples from people presenting to a large number of UK NHS hospitals and there is currently no viable mechanism for establishing all UK hospitals as research sites.

Provision of samples for research purposes without specific consent is considered ethically justifiable because

- The study involves the study of biological samples that have already been provided for similar clinical purposes (identification of recreational drugs, including traditional illegal drugs)
- More detailed analysis of samples may reveal NPS associated with toxicity and this has potentially important benefits for recreational drug users in general

- Identification of NPS can be fed back to the Toxicology lab and subsequently to the clinical team managing the person with suspected drug toxicity. Although this will only be of clinical value in a small number of people with prolonged features, this may occasionally prevent other investigations being performed.
- Results will be of interest to the drug user and the clinicians involved in management.
- Samples are suitably anonymised so cannot be identified except by the toxicology laboratory supplying the sample. The HPRU research team will not be able to identify the individual, although the linked-anonymised design allows the local NHS laboratory to contact the responsible clinical team to clarify clinical information or to feed back results of clinical relevance as needed.

Data provided with the sample(s)

NHS laboratories are able to provide data as supplied to them on the original request form and the following will be provided to the research team with the biological samples:

- Date and time of sample
- Age and sex of drug user
- Postcode of drug user's NHS registered address (first 4 digits)
- Treating hospital
- Reported clinical features

Study 4. Collection of samples for research purposes from people attending participating emergency departments

Potential limitations of restricting the research to samples collected for clinical purposes are

(a) It may not be considered clinically necessary in individual patients for samples to be sent for toxicology screening, even if severe toxicity is present.

(b) It may be difficult to obtain detailed clinical information to link with results of analyses, as the information available is restricted to that provided on the request form (although some clarification between the NHS lab and the requesting clinician may be possible).

For this reason, it is appropriate to collect samples (blood, urine, oral fluid, the remainder of substances taken) from people presenting to acute NHS hospitals with severe toxicity associated with suspected NPS use, with informed consent from those with capacity. This allows the collection of high quality and more complete clinical information according to a pre-specified protocol and also allows clarification of detail directly between the local clinician/researcher and the central research team. Multiple samples may be provided from the same patient, if available and consent has been provided, so that pharmacokinetic and pharmacodynamic information can be collected, including half-life of the parent drug implicated and the formation of metabolites.

While it would be ideal if every UK emergency department was set up as a research site to provide a comprehensive UK-wide coverage, this is not feasible within the financial and administrative resources available. Therefore, this research aspect will involve a restricted number of selected emergency departments where there is a local researcher willing to lead the research in that centre. This will initially be a small number of departments (approximately 10), but the number is expected to grow as the research progresses.

Study 4 **Inclusion criteria**	**Exclusion criteria**
• Patient with suspected recreational drug exposure • Presence of severe acute toxicity (See text) • Patient consent (immediate or retrospective)	• Refusal of consent • Absence of severe toxicity • Children and young people <16 y • Samples collected for investigation of suspected non-accidental injury

Patients with any of the features listed in the table below at any time after presentation (in the absence of another identified cause) will meet study criteria for acute severe toxicity. These criteria will be kept under review and updated as needed as the study progresses:

TABLE: Criteria for severe toxicity (present at any time after exposure)

• Fever > 38.5 ^{o}C • Glasgow coma scale < 8[a] • ITU/HDU admission • Requirement for intubation and ventilation • Seizures • Hallucinations/psychosis • Prolonged behavioural disturbance (> 24 h) • Arrhythmia • Chest pain or ECG evidence of cardiac ischaemia	• Acidosis (arterial or venous pH < 7.35) • Tachycardia > 140 /min • SBP > 180 mmHg • SBP < 80 mmHg • Acute kidney injury[b] • Creatine kinase activity raised (> 1000 IU/L) • ALT/AST activity > 300 IU/L • PT > 15 s or INR > 1.3 • Death • Poisons Severity Score[61] of 3 (Severe)

[a]In the absence of likely alternative causes (e.g. severe alcohol intoxication, use of sedative drugs etc).

[b]Defined as a rise in serum creatinine of ≥26 micromol/litre within 48 hours, a 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days, or a fall in urine output to less than 0.5 ml/kg/hour for more than 6 h[63]

Recruitment and consent arrangements

People meeting the inclusion criteria will be identified by the responsible clinician, who will assess capacity to make a decision about participation in the research. This will occur as soon as possible after admission. It will be assumed that a potential participant has capacity unless there is proof that they do not have capacity for this specific decision, as provided by the capacity assessment made by clinical team.

Potential participants with capacity

If the potential participant has capacity and is willing to discuss the research, they will be seen by a member of the local research team who will verify inclusion and exclusion criteria, explain the study and give them a participant information sheet (Appendix 3) and consent form (Appendix 4). The potential participant will be given the time they need to decide if they are willing to participate and to sign the consent form. It is important to collect initial samples as soon as possible after presentation, but if the potential participant would like more time to consider their decision, it is still possible to include them in the research as they may subsequently consent to previously taken clinical samples held routinely in the NHS lab being used for the research.

Potential participants lacking capacity

Impaired capacity is common in the target participant group because of drug/alcohol intoxication, but it is important that these patients are included in the research as they constitute a more severely affected cohort. Restricting the study to participants with capacity to give consent would substantially reduce the capability of the research to identify rapidly those NPS associated with serious toxicity. Inclusion of patients lacking capacity will entail little or no discomfort, as additional venepuncture for research purposes, in advance of consent, is not proposed.

If capacity is not present it is proposed that residual blood from samples taken for clinical purposes and non-invasively collected oral fluid and/or urine samples are stored locally until the patient regains capacity, at which time delayed consent for provision of these samples for the research, together with the necessary clinical data, can be sought. If consent is refused the samples would be not be used for the research. The justification for collection of samples in

advance of consent is that this is time critical, needing to occur as soon as possible after admission, before plasma drug concentrations fall as a result of metabolism and excretion. Note that early blood sampling is part of the routine clinical care of patients presenting with drug toxicity ands storage of residual clinical samples in case of the need for further/repeated analysis is standard practice in NHS biochemistry laboratories.

These consent arrangements allow the study to be discussed directly with the potential participant and for informed consent to be obtained before samples are used for research. This discussion can occur at the time of blood/urine/oral fluid sampling if the potential participant is considered to have capacity, but when necessary, this discussion can be delayed until capacity is restored.

There will be a small number of potential participants who have impairment of capacity that persists, including patients who require prolonged ventilation. In the event of fatal toxicity it is possible that capacity would not be present at any time between presentation and death. Under these circumstances of very severe toxicity, the analysis for responsible NPS is of critical importance.

It is therefore proposed that for research sites in England and Wales, if after at least 12 hours capacity has not been regained, support for inclusion of the potential participant will be sought from a consultee, consistent with Department of Health Guidance and Section 32(3) of the Mental Capacity Act 2005,[b] using arrangements approved by a Research Ethics Committee. This would be a personal consultee if available, i.e. a person who knows the person lacking capacity well, but is not acting in a professional or paid capacity, such as a family member, non-paid carer or friend. If an appropriate personal consultee cannot be identified after reasonable steps have been taken, a nominated consultee (or Professional Legal Representative, PLR) will be approached. Arrangements for nominated consultees will be made locally in research sites, in accordance with DH guidance. Advice on inclusion of the potential participant in the research will be sought using the *Participant Information Sheet* (Appendix 3) and recorded using a *Consultee Declaration Form* (Appendix 5).

[b] http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_083133.pdf

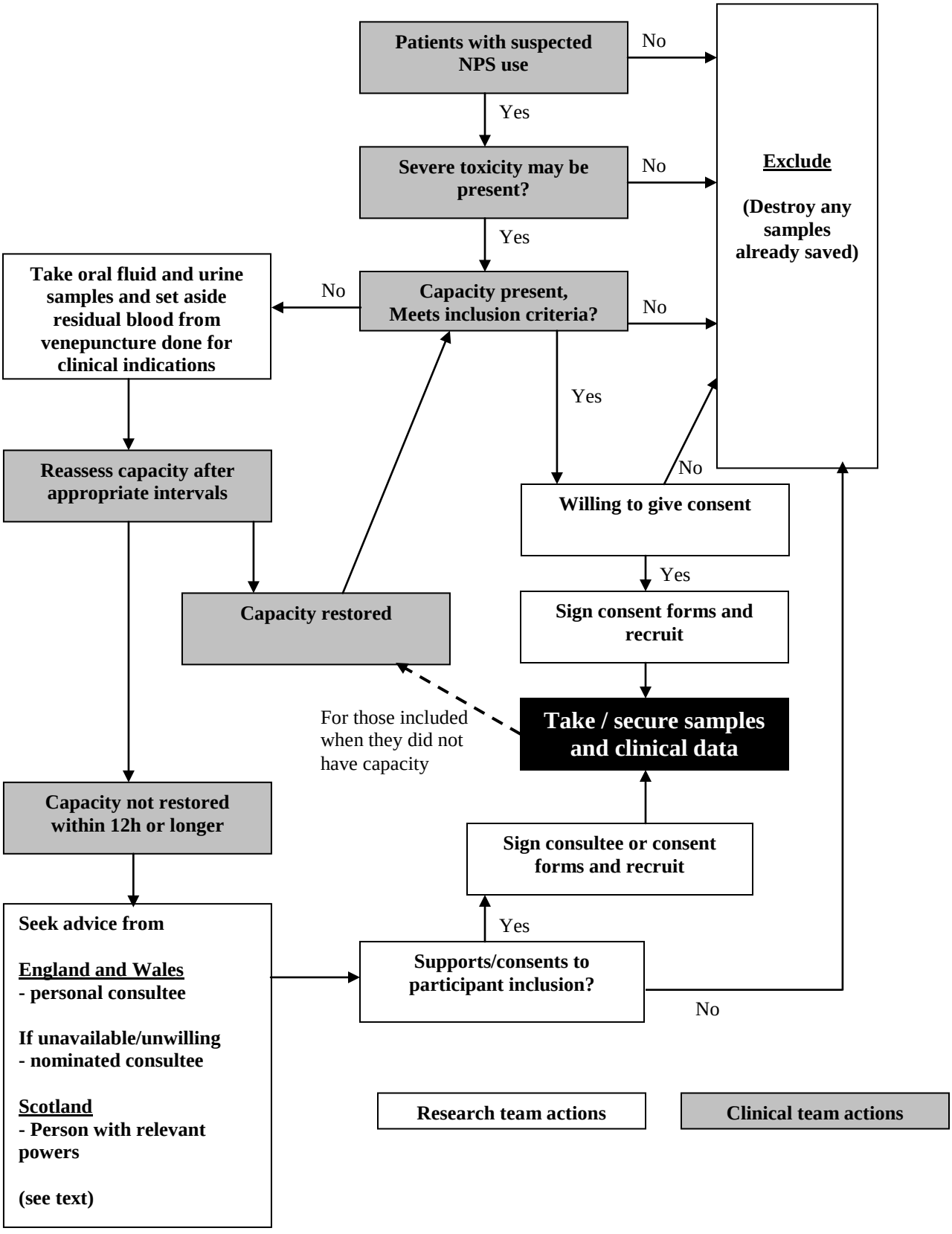
For research sites in Scotland, arrangements will be consistent with the Adults with Incapacity (Scotland) Act 2008. Consent will be sought from a person with relevant powers (i.e. their guardian, welfare attorney or closest family member if these have not been appointed). Consent for inclusion of the potential participant in the research will be sought using the *Participant Information Sheet* (Appendix 3) and recorded using the *Consent Form (Person with relevant powers)* provided in Appendix 6.

Note that, irrespective of the advice of consultees (England and Wales) or consent provided by people with relevant powers (Scotland), potential participants without capacity will be informed about the research in as clear and appropriate a way as possible and those that express objections to participation will be not be included.

In the event of capacity being restored, participants will be asked for consent to continue in the study and this decision will be supported by the participant information sheet (Appendix 3). They will be given the option to consent to remain in the study, to decline consent but to allow data and samples already collected to be used for the research or to decline consent and refuse permission. A consent form is available to record this decision (Appendix 7).

For patients with fatal toxicity, toxicological screening may be carried out as part of the Coroner's (Procurator Fiscal in Scotland) investigation and this would take precedence over this research. The clinical and research teams involved would provide samples or analysis results to the Coroner/ Procurator Fiscal as requested. Collation of post mortem toxicology data from coroner's inquests is not a focus of this project as this has been undertaken by the npSAD study. Recruitment, capacity and consent arrangements are summarized in the algorithm below.

Recruitment algorithm



Schedule of events (Study 4)

Action	Clinical or research?	Notes	n*
Identification of patient with suspected acute severe NPS toxicity	Usual clinical practice	All potential participants	200
Capacity assessment	Usual clinical practice	All potential participants	200
Taking consent	Research	Participants with capacity or when capacity restored within 12 h	175
Identification and consent/agreement fromconsultee/person with relevant powers	Research	Participant without capacity for more than 12h	25
Blood sample 1	Usual clinical practice	Additional blood may be taken for research purposes at time of clinically indicated venesection	200
Urine sampling 1	Research		200
Oral fluid sampling 1	Research		200
Reassessment of capacity	Usual clinical practice		100
Consent from person previously entered when they did not have capacity	Research		25
Completion of data collection sheet	Research	See Appendix 2	
Blood sample 2	Usual clinical practice	Patients with persisting toxicity	50
Urine sampling 2	Research	Patients with persisting toxicity	50
Oral fluid sampling 2	Research	Patients with persisting toxicity	50
Blood sample 3	Usual clinical practice	Patients with persisting toxicity	25
Urine sampling 3	Research	Patients with persisting toxicity	25
Oral fluid sampling 3	Research	Patients with persisting toxicity	25
Blood sample 4**	Usual clinical practice	Patients with persisting toxicity	10
Urine sampling 4**	Research	Patients with persisting toxicity	10
Oral fluid sampling 4**	Research	Patients with persisting toxicity	10

***** Estimated for 10 research sites over 4 years

** Further samples may be taken in a small number of patients with prolonged persisting toxicity

Data provided

As well as biological samples (described above), research sites will supply demographic and clinical information using a structured data collection form (Appendix 2).

Confidentiality and data protection

All identifiable data used in the research will be held in the Newcastle Hospitals NHS Foundation Trust, with electronic data stored on password protected computers. Processing of data will be subject to standard NHS data protection policies with approval from the Trust Caldicott Guardian. As for all NHS staff, those with access to the data will be subject to NHS policies and procedures for information governance. Fully anonymised research results will be shared with research partners as needed for analysis, interpretation and writing up of reports and papers.

It is acknowledged that there is a theoretical risk of inadvertent identification of patients, for example by triangulating the clinical information collected with media reports that might identify an individual. The study team will take all reasonable steps to minimize this risk.

Study 1

The NPIS database (UKPID) contains identifiable sensitive data from clinical enquiries and is registered with the Caldicott guardians of all 4 participating NHS Trusts. Data used for the research will be downloaded into a separate database in linked-anonymised format with the permission of the data controllers of each participating NHS Trust. Researchers processing the data (e.g. for epidemiology or modeling purposes) will only have access to fully anonymised data from that database and will therefore not be able to identify individual patients. Use of linked anonymised ('pseudonymised') data in this format for research purposes without consent is consistent with current MRC guidance as the researchers are unable to identify the individuals involved.[c]

[c] Medical Research Council. Data and Tissues toolkit. Consent arrangements: should consent be sought? http://www.dt-toolkit.ac.uk/routemaps/station.cfm?current_station_id=427

Study 2

This involves the provision of linked anonymised data on positive samples from participating NHS toxicology Laboratories. These will include patient age and sex, home post code (first 4 digits only), information provided on clinical features (without identifiers) as reported on the original NHS request form and results of toxicology screening. Use of these data without consent is consistent with MRC guidance, as for Study 1.

Study 3:

The data provided to the central research team in Newcastle will include patient age and sex, home post code (first 4 digits only), information provided on clinical features (without identifiers) as reported on the original NHS request form, results of toxicology screening, the nature and timing of the exposure and the timing of sample collection. Data held by the research team will be identified only by a laboratory number, which acts as the link between the data and the identity of the patient; this link is held by the local NHS toxicology laboratory and the central research team will have no access to that. Use of these data without consent is consistent with MRC guidance, as for Study 1. Similarly, for tissue samples (blood, urine, oral fluid), MRC guidance and the Human Tissue Act 2004 state that exceptions to the need for consent apply when material is collected from living persons (when the sample is taken), are anonymous[d] and the research project is approved by an NHS Research Ethics Committee.

Study 4: Collection of samples for research purposes

Clinical records will be retained by the local researcher. Information passed on to the research team in Newcastle will include a study number, the age, sex and postcode (first 4 digits) of the patient, the nature and timing of the exposure, the timing of sample collection and the recorded clinical features (using a structured data collection form as shown in Appendix 2). The great majority of samples and data will be provided with consent in place at the time of transfer to the research team, but there will be a small number of samples collected without consent from adults

[d] The Human Tissue Authority consider that tissue is anonymised if the researcher is not in possession, and is not likely to come into possession, of information from which the individual can be identified. This does not mean that samples must be permanently unlinked, and coding samples meets these requirements.
http://www.dt-toolkit.ac.uk/glossary.cfm?cit_id=0&startLetter=A

with incapacity. Arrangements are in place to allow this by means of appropriate declarations from personal or nominated consultees (England and Wales) or consent from persons with relevant powers (Scotland).

Statistical aspects

Information on expected numbers of patients and samples are provided in the Table below. There is uncertainty about the amount of data that may be available for studies 2-4 and these numbers will be updated as necessary by a protocol amendment as the study progresses.

Descriptive statistics will be used for studies 1 and 2 and will characterize the epidemiology of poisons service enquiries about NPS and of positive toxicology screening samples handled in NHS Toxicology laboratories.

For studies 3 and 4, formal statistical analysis is unlikely to be required. Useful data linking particular features of toxicity with analytical conformation of exposure is valuable even if this is achieved in a single patient.

No hypothesis testing, e.g. comparing toxicity between agents, is envisaged for data collected in any of the studies and as such formal power calculations are not needed.

Table : Estimated sample sizes

Study	**Annual numbers expected (overall)**
1. NPIS data (a) Telephone enquiries (b) TOXBASE accesses	 1550 drug of misuse, 400 NPS/ 'Legal High' 55,000 drug of misuse, 5,000 NPS/'Legal High'
2. NHS Toxicology labs – data from screening	1000 (estimated) anonymised screening results
3. Samples from NHS toxicology labs	50 (estimated) from patients with acute toxicity
4. Samples from research sites	50 (estimated) from patients with acute toxicity

Research approvals

Ethical approval for the study will be sought from a Research Ethics Committee. Research Management and Governance approvals will be sought as appropriate from participating NHS organizations (NHS Trust Emergency Departments participating in study 4 and NHS Trust Toxicology laboratories participating in studies 2-4).

As part of this process, appropriate Material Transfer Agreements will be arranged to allow transfer of biological samples between research sites. These samples will be kept in accordance with local policies and destroyed once analysis has been completed or within 1 year of the end of the 5 year research project (whichever is the earliest). A license from the Human Tissue Authority is not needed for storage of samples collected with ethical approval.

Analytical methods

Blood, plasma, urine and oral fluid samples will be analysed for a range of psychoactive substances using modern mass spectrometric based techniques. A major challenge for the analysis of novel psychoactive substances is that new substances with unknown metabolites are constantly emerging. A combination of targeted screening – Multiple Reaction Monitoring, precursor and neutral loss ions scans – and high resolution data dependent and data independent methodologies will be utilized, using triple quadrupole, ion trap and time of flight mass spectrometers, to provide a comprehensive profile of the emerging psychoactive substances and their metabolites. Psychoactive substances and metabolites will be identified using an integrated workflow incorporating qualitative exploration, rapid profiling and data interrogation using metabolomic software.

Evaluation of certified analyte reference standards is required for validating methodology. Up to date blood, plasma and urine analytical methods, targeting as many NPSs for which reference standards are currently available, are critical to effectively monitoring NPSs. In addition, these reference materials will be used to create and customise a NPS mass spectral library data base for fast and effective identification and confirmation of unknown compounds.

Nominal-mass multiple reaction monitoring (MRM) triggered product ion spectra detection will be employed for targeted compounds using triple quadrupole or hybrid triple quad-linear ion trap instruments. However, high-resolution and accurate mass tandem MS using time of flight mass spectrometers provide accurate mass information on both the parent molecule and fragment ions, affording greater specificity and potentially simplifying data interpretation. Novel non-targeted analytical techniques using a LC-QqTOF high-resolution tandem mass spectrometer will be employed to identify novel NPSs and their metabolites. Both data dependant and data independent non-targeted methodologies will be developed. The data independent methods will employ SWATH acquisition (Sequential Windowed Acquisition of all THeoretical mass spectra), which sequentially acquires MS/MS of all precursor ions across a specified mass range, by breaking down the mass range into small windows.[62] In every scan cycle, the instrument rapidly and sequentially acquires MS and MS/MS of all mass windows across the specified mass

range. Since the approach is non-targeted, it should not require future modifications for incorporating newly emerging compounds, and MS and MS/MS spectra acquired for unknown compounds can be identified retrospectively via data re-interrogation against the reference spectra in the in-house data base.

Once a new drug has been identified and an appropriate standard is available, this can be added to the targeted screening using LC-MS/MS performed in Toxicology laboratories.

Mathematical and modelling methods

NPIS telephone and TOXBASE enquiries and positive toxicology laboratory samples will be used as indices of NPS use. Temporal trends in both types of enquires will be analysed using time series analyses undertaken at short sample periods, which will be used to alert the HPRU to trends in use. Bayesian disease mapping techniques will be used to analyse spatial and temporal trends in records for NPS. Area-based autoregressive modeling (CAR models) will identify spatial variation in NPS use across the study area, whilst also highlighting potential risk factors (socio-economic status, age distribution etc). State-space time series analysis will be used to investigate the impact of drug control policies and the interplay between telephone and web enquiries.

Dissemination of research results

Research outputs will be discussed with the steering group and reported to the NIHR as funder of the research on an annual basis. Important research findings will be provided to official organizations such as the UK Focal Point, ACMD and EMCDDA, presented at scientific meetings and submitted for publication as appropriate.

Information obtained by the research will be used to inform NPIS guidance for NHS health professionals published on TOXBASE.

Communication of research findings to the general public and particularly potential NPS users is of great importance. This will be achieved via the study website, by articles in the lay media and via local Drug and Alcohol Action Teams. The project is developing robust arrangements for patient and public involvement (PPI) for designing, conducting and reporting the research and this expertise will be used in disseminating research results.

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APPENDIX 1: Classification of NPS and related traditional recreational drugs

Major group	Subgroup	Examples
Synthetic Cannabinoid Receptor Antagonists (SCRAs)[18, 19, 21, 22, 64]	1st generation	JWH-018, HU-210
	2nd generation	AM2201, AM1220, RCS4, UR-144, XLR-11
	3rd generation	APICA, STS-135, BB-22, LY2183240
Opioids[24]		desomorphine, MT-45
Benzodiazepines[14]		Etizolam, diazepam, phenazepam
Indolealkylamines (tryptamines)[9, 65, 66]		Dimethyltryptamine, 4-hydroxy,N,N-dimethyltryptamine (Psilocin), alphamethyltryptamine (AMT)
Piperazines[12, 67-70]		e.g. Benzylpiperazine (BZP), mCPP
Arylcyclohexamines[15, 16, 71, 72]		Ketamine, methoxetamine, PCP
Phenylethylamine derivatives*	Amphetamines	Amphetamine, methamphatamine, 4-methylamphetamine, PMA, PMMA
	Cathinones[2, 50, 73-76]	mephedrone, 3-methylmethcathinone, α-PVP, methylone
	Benzofurans and difurans[4, 5]	5-APB, bromodragonfly
	Aminoindans[77-80]	2-AI, 5-IAI, MDAI
	D-Series[81],	DOB, DOM
	2C-series	2C-B, 2C-E
	NBOMe compounds[6-8, 82-84]	25I-NBOMe
	Methylenedioxy amphetamines	MDMA, MDA
Piperidines and pyrrolidines[52, 85-87]		D2PM, 3,4-dichloromethylphenidate
Plant extracts		Kratom[88], Salvia,[89] ibogaine[90]
Others		4,4-DMAR,[91] Ethaqualone, 2-MeO-Diphenidine, methoxphenidine, mephtetramine,[92] cocaine.

* Overlaps in the structural classification exist such that some chemicals may belong to more than one group. For abbreviations see p6.

APPENDIX 2: Clinical data collected (Study 4)

PRESENTATION DETAILS
Local ID/Lab number
Age (years)
Sex
Date of presentation
Time of presentation

EXPOSURE DETAILS
Reported exposure(s)
Date of exposure
Time of exposure
Type of exposure
Route of exposure
(*tick all that apply*)

Acute	☐	Chronic	☐
Oral/ingested	☐	IV	☐
Insufflated	☐	IM	☐
Snorted	☐	SC	☐
Smoked	☐	Multiple	☐
Other	☐		

CLINICAL FEATURES	No	Yes persisting	Yes resolved	Comments
General				
Pyrexia (fever)	☐	☐	☐	Max Temp (ºC):
Hypothermia	☐	☐	☐	Min Temp (ºC):
Abnormal sweating	☐	☐	☐	
Other	☐	☐	☐	
Gastrointestinal	☐	☐	☐	
Vomiting	☐	☐	☐	
Abdominal pain	☐	☐	☐	
Bleeding	☐	☐	☐	
Other	☐	☐	☐	
Neurological				
Reduced conscious level	☐	☐	☐	Min GCS:
Seizure	☐	☐	☐	
Mydriasis (dilated pupils)	☐	☐	☐	
Miosis (small pupils)	☐	☐	☐	
Hypertonia	☐	☐	☐	
Hypereflexia	☐	☐	☐	
Clonus	☐	☐	☐	
Dystonia	☐	☐	☐	
Tetany	☐	☐	☐	
Other	☐	☐	☐	

CLINICAL FEATURES	No	Yes persisting	Yes resolved	Comments
Cardiorespiratory				
Bradycardia (HR<60)	☐	☐	☐	Min HR:
Tachycardia (HR>100)	☐	☐	☐	Max HR
Hypertension (SBP>160)	☐	☐	☐	Max SBP:
Hypotension (SBP<80)	☐	☐	☐	Min SBP:
Dizziness	☐	☐	☐	
Arrhythmia	☐	☐	☐	Type:
Palpitations	☐	☐	☐	
Chest pain	☐	☐	☐	
Breathing difficulties	☐	☐	☐	
Other	☐	☐	☐	
Psychiatric				
Agitation	☐	☐	☐	
Aggression	☐	☐	☐	
Confusion	☐	☐	☐	
Hallucination	☐	☐	☐	
Paranoid ideation/Psychosis	☐	☐	☐	
Depression	☐	☐	☐	
Suicidal ideation	☐	☐	☐	
Catatonia	☐	☐	☐	
Other	☐	☐	☐	

LAB FINDINGS	No	Yes persisting	Yes resolved	Comments
Acidosis	☐	☐	☐	Min pH:
Hyponatramia	☐	☐	☐	Min Na^+
Hypokalaemia	☐	☐	☐	Min K^+
Hyperkalaemia	☐	☐	☐	Max K^+
Other (specify in comments)	☐	☐	☐	

TREATMENT GIVEN	Yes	No	Comments
Activated charcoal	☐	☐	
Whole bowel irrigation	☐	☐	
Cyproheptadine	☐	☐	
Dantrolene	☐	☐	
Intubation	☐	☐	
Ventilation	☐	☐	
Cooling measures	☐	☐	
Extracorporeal therapy	☐	☐	
Other	☐	☐	

LAB FINDINGS	No	Yes persisting	Yes resolved	Comments
Creatinine increased	☐	☐	☐	Max Creat:
ALT/AST activity increased	☐	☐	☐	Max ALT/AST:
CK activity increased	☐	☐	☐	Max CK:
PT increased	☐	☐	☐	Max PT:
Other (specify in comments)	☐	☐	☐	

OUTCOME	Date	Time	LOS	Comments
Discharged				
Transferred				To:
Died				
Other				

SAMPLING		Date	Time	Comments
Blood	☐			
Plasma	☐			
Urine				
Oral fluid				

APPENDIX 3: Participant information sheet (Study 4)

Identification and characterization of the clinical toxicology of novel psychoactive substances (NPS) by laboratory analysis of biological samples from recreational drug users.

You are invited to take part in a research study. To help you to decide, it is important that you understand why the research is being carried out and what it will involve for you. One of the research team will go through the information sheet with you and answer any questions that you have. Please take the time to read the following information carefully, and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Please start by reading the study summary. If you think you might be interested in taking part, please go on to read the remainder of this information sheet.

STUDY SUMMARY

There has been increasing recent use of newer recreational drugs. These are officially termed 'Novel Psychoactive Substances' or NPS, but also sometimes called 'legal highs' or 'research chemicals'. A large number of different substances have been involved and some of these have caused severe adverse effects in users, requiring hospital admission. It is important to identify the substances that are causing adverse effects as quickly as possible so that steps can be taken to inform and protect people who might consider using these drugs.

You are being asked to take part in this study because you have experienced adverse effects that could be caused by a recreational drug.

If you agree, we will ask you to provide urine and/or oral fluid (saliva) specimens and some additional blood, which will usually be some left over from samples already taken from you as part of your clinical care. These will be sent to a research laboratory for analysis, together with information about any adverse effects you have experienced. If you have any of the substance you have taken left over and you are willing, this can also be sent for analysis.

We also want to send details about you and your symptoms to the research laboratory, together with your samples. Note that the laboratory receiving your samples and information will not be able to identify who you are. By analyzing your samples, we hope to find out what substances may have been causing the adverse effects that you have experienced.

Other than providing the samples, you do not have to do anything else. The study does not affect your usual clinical treatment.

If you are interested in taking part in the study, please continue to read the rest of this information sheet.

PARTICIPANT INFORMATION SHEET

Identification and characterization of the clinical toxicology of novel psychoactive substances (NPS) by laboratory analysis of biological samples from recreational drug users.

Part 1 – Study specific details

What is the purpose of the study?

In recent years there has been increasing use of a group of new recreational drugs called 'Novel Psychoactive Substances' or NPS, sometimes also called 'legal highs' or 'research chemicals.' A large number of these substances have been sold to users via the internet, 'head shops' and by dealers. As these substances are new, there is usually no information about safety of use in humans. Some people who have taken these drugs have experienced severe adverse effects requiring hospital treatment and some people have died, although this is probably very uncommon.

It is important to find out the substances involved when people develop severe adverse effects after recreational drug use. This means that actions can be considered to protect people who might consider using substances associated with danger. Such steps might include warnings to users or legal control ('banning' the specific substance).

In this study we want to collect blood, urine and or saliva samples, together with clinical details, from people experiencing severe adverse effects after use of recreational drugs so that we can identify the chemicals that may be responsible and study the adverse effects that they may cause.

Why have I been chosen?

You have come to hospital with symptoms that may have developed as a result of the use of a recreational drug, such as a 'legal high'. We want to find out precisely which drugs may have caused your symptoms by analyzing your blood, urine and/or oral fluid (saliva) to see what drugs may be present.

Are there any criteria I need to meet before I can take part in the study?

We want to include people in this research if they have taken a recreational drug and have experienced adverse effects. If you feel this does not apply to you, please tell us.

Are there any reasons I couldn't take part?

It is not possible to take part if you are less than 16 years old, you have not used a recreational drug or legal high recently or if you have not experienced any adverse effects. If these apply to you, please tell us.

Do I have to take part?
It is up to you whether you decide to take part and you do not have to participate if you do not wish to. However, if you do decide to participate, we will explain to you what is involved and give you this information sheet to keep. You will be asked to sign a consent form; before you do that, you can be given time to think this over and talk to your family and friends about it if you wish. If you decide to take part, you are still free to withdraw from the study at any time, and you do not have to give a reason. This will not influence the treatment or standard of care that you receive, either now or in the future.

What will happen to me if I take part?
If you agree to be part of the study, the researcher will use part of blood samples that are being taken as part of your routine clinical care. They will also ask you to provide urine and saliva specimens. You can also provide a sample of the substance you have taken (e.g. a tablet, powder, blotter etc) if you are willing and this is available. Most patients will provide only one blood or urine sample, but further samples may be used, especially if your symptoms are continuing.

What do I have to do?
Other than providing the blood and urine specimens, you do not have to do anything. You can leave hospital as usual when you are well enough.

What are the possible benefits of taking part?
It is possible that the research will identify the chemical name(s) of any drug(s) or legal high(s) that are in your blood or urine. This may help your doctors to treat you or advise you on how long your symptoms may last. However, we cannot guarantee that the research will identify any drugs in your blood or urine, or that the results will be available while you are still in hospital.

Part 2 – General information

Travel Expenses
Blood and urine samples are taken while you are still in hospital so you will not have any additional travel or other expenses.

What will happen if I don't want to carry on with the study?
If you decide that you don't want to provide further samples, tell the researcher who will comply with your wishes. If you decide you no longer want your blood or urine sample to be used for the research, you can also tell the researcher. He/she can arrange for your samples to be discarded, provided they have not already been analysed. If they have been analysed the results of that will not be discarded, but all links between you and the results will be destroyed, so that no one will be able to tell that the results come from you.

What if there is a problem?
If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions. You can do so by contacting xxxxx (on the contact details found at the end of this form). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details of how to complain can be obtained by contacting your local Patient Advice and Liaison Service officers:

Insert local details

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation; however, but you may need to meet your own legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). NHS Indemnity does not offer no-fault compensation (i.e. for harm that is not anyone's fault). Neither the sponsor (XXX NHS Foundation Trust) who has undertaken to manage the study, nor the management of the hospital/research centre you are attending for your treatment, is able to agree in advance to pay compensation for non-negligent harm. They may, however, consider an ex-gratia payment in the case of a claim.

Will my taking part in the study be kept confidential?
If you take part in this study, research staff will collect personal data about you and this will be regarded as strictly confidential. All study files will be kept securely locked away on the study site and will only be accessed by the research personnel involved in the study. Non-personal data will be entered onto a secure database. Access to this database will be password-protected and available to doctors and research staff, for the purpose of the study. All data stored on the computer will be coded and your name will not be used. You will be given a unique study number which will be shown on all data and test results.

Your medical records may be looked at by representatives of regulatory authorities and by authorized people from the Trust to monitor the study and ensure that it is being carried out correctly. Everyone who sees data has a duty to ensure that nothing that could reveal your identity is disclosed outside the research site. Results of analysis will not be provided to the police.

All the information about your participation in this study will be kept confidential, and all data will be stored for at least 10 years and then disposed of securely.

Involvement of your General Practitioner
We will not routinely notify your GP that you have taken part in the study, but your participation will be noted in your hospital/medical records. We ask your permission to inform the clinical team looking after you in hospital if we find anything that may have consequences for your health. This information will be passed on to you. It may also be provided to your GP if considered clinically necessary.

What will happen with any samples?
The blood and urine samples that you give will be sent to the Research laboratory at Newcastle University for analysis, together with the clinical information about you. Any important findings will be returned to your usual clinician, as with any other clinical specimen. All samples will only be labeled with your unique study code rather than your personal details. This means that the research team in Newcastle will not be able to identify who you are.

What will happen to the results of the research study?
We will publish the results of the study in scientific journals. We will also present the findings at international meetings and to patient groups which have been involved in the design of this study and taken part in it. None of this material will include details that might identify people who took part in the research.

Who is organizing and funding the research?
The research is being organised by the Newcastle University Health Protection Research Unit and is supported by a grant from the National Institute for Health Research.

Who has reviewed the study?
All research in the NHS is reviewed by an independent group of people, called a Research Ethics Committee. This study has been reviewed and approved by the Newcastle and North Tyneside 1 Research Ethics Committee. The Chief Executive of the xxx NHS Foundation Trust has agreed to provide indemnity for the study in terms of its management. The conduct of the study at participating NHS Trusts, in terms of your treatment, has indemnity cover through the normal NHS schemes.

The NHS is trying to improve clinical and research standards. This is being achieved through 'clinical governance'. As part of this process, this study may be reviewed by a clinical governance team. Such a team would need to look at any information that you provide us with, to make sure that the research was carried out in accordance with proper procedures.

Contact names and telephone numbers for further information

For any concerns or questions about this study, please contact:

Study Doctor:	***Study Nurse:***
insert	**insert**

For any concerns about your rights as a participant or any complaints, please contact:

Patient Advice and Liaison Service (PALS) – telephone: insert

Before you sign the informed consent form, you should ask questions about anything that you do not understand. The study staff will answer any questions before, during and after the study.

Thank you for taking the time to read this information sheet.

APPENDIX 4: Participant informed consent form

Version 1.3, 5th January 2015

Identification and characterization of the clinical toxicology of novel psychoactive substances (NPS) by laboratory analysis of biological samples from recreational drug users.

Consent Form

Name of Lead Researcher: Dr

Please initial box

1. I confirm that I understand the nature of the study proposed, having read and understood the information sheet provided (Version 1.3, 5th January 2015). I have had opportunity to ask questions, and I am satisfied with the answers I have received. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the participating or sponsoring NHS Trusts or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the study ☐

_____	____/____/____	_____
Name of participant (please print)	Date	Signature
_____	____/____/____	_____
Name of person taking consent (please print)	Date	Signature

When completed: one copy to patient; original copy to Site Investigator File; one copy for medical records. THANK YOU

APPENDIX 5: Consultee declaration form (England and Wales)

Version 1.3, 5th January 2015

Identification and characterization of the clinical toxicology of novel psychoactive substances (NPS) by laboratory analysis of biological samples from recreational drug users.

Consultee declaration Form

Name of Lead Researcher: Dr

Name of potential participant

Please initial box

1.	I understand that I am being consulted about [name of potential participant]'s participation in this research project because he/she is not currently able to consent for him/herself	☐
2.	I have read and understood the information sheet provided (Version 1.3, 5th January 2015). I have had the opportunity to ask questions about the study and understand what is involved.	☐
3.	I understand that participation is voluntary and that that he/she is free to withdraw at any time, without giving any reason, without his/her medical care or legal rights being affected. I also understand that they will be asked to give consent for themselves or decline participation when they are able.	☐
4.	I understand that sections of his/her medical notes may be looked at by responsible individuals from the participating or sponsoring NHS Trusts or from regulatory authorities where it is relevant to him/her taking part in research.	☐
5.	In my opinion he/she would have no objection to taking part in the above study.	☐

_____ ____/____/____ _____

Name of consultee (please print) Date Signature

Relationship to participant _____

_____ ____/____/____ _____

Person undertaking consultation (please print) Date Signature

When completed: one copy to patient; original copy to Site Investigator File; one copy for medical records. THANK YOU

APPENDIX 6: Consent form (person with relevant powers, Scotland)

Version 1.3, 5th January 2015

Identification and characterization of the clinical toxicology of novel psychoactive substances (NPS) by laboratory analysis of biological samples from recreational drug users.

Consent Form

Name of Lead Researcher: Dr

Name of potential participant

Please initial box

1.	I understand that, as a person with relevant powers, I am being asked to give consent to [name of potential participant]'s participation in this research project, because he/she is not currently able to consent for him/herself	☐
2.	I have read and understood the information sheet provided (Version 1.3, 5th January 2015). I have had the opportunity to ask questions about the study and understand what is involved.	☐
3.	I understand that participation is voluntary and that that he/she is free to withdraw at any time, without giving any reason, without his/her medical care or legal rights being affected. I also understand that they will be asked to give consent for themselves or decline participation when they are able.	☐
4.	I understand that sections of his/her medical notes may be looked at by responsible individuals from the participating or sponsoring NHS Trusts or from regulatory authorities where it is relevant to him/her taking part in research.	☐
5.	In my opinion he/she would have no objection to taking part in the above study and I consent to him/her taking part.	☐

_____ ____/____/____ _____

Name of person with relevant powers (please print) Date Signature

Relationship to participant _____

_____ ____/____/____ _____

Person taking consent (please print) Date Signature

When completed: one copy to patient; original copy to Site Investigator File; one copy for medical records. THANK YOU

APPENDIX 7: Consent form (Person previously included when they did not have capacity)

Identification and characterization of the clinical toxicology of novel psychoactive substances (NPS) by laboratory analysis of biological samples from recreational drug users.

Consent Form

Version 1.3, 5th January 2015

Name of Lead Researcher: Dr

		Please initial box
1.	I understand that I was included in this research study at a time when I was not able to make my own decision about my participation. I am now being asked if I consent to remaining in the study.	☐
2.	I have read and understood the information sheet provided (Version 1.3, 5th January 2015). I have had the opportunity to ask questions about the study and understand what is involved.	☐
3.	I understand that participation is voluntary and that that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected	☐
4.	I understand that sections of my medical notes may be looked at by responsible individuals from the participating or sponsoring NHS Trusts/Boards or from regulatory authorities where it is relevant to him/her taking part in research.	☐

Please turn over

Identification and characterization of the clinical toxicology of novel psychoactive substances (NPS) by laboratory analysis of biological samples from recreational drug users.

Consent Form (Continued)

Version 1.3, 5th January 2015

Please choose <u>one</u> the following 3 options by initialing the appropriate box

1. I consent to remain in the study ☐

OR

2. I do not consent to remain in the study, but I consent to my data and samples taken so far to be used for the research ☐

OR

3. I do not consent to remain in the study, and I do not consent to data and samples taken so far to be used for the research ☐

_____	____/____/____	_____
Name (please print)	Date	Signature

_____	____/____/____	_____
Person taking consent (please print)	Date	Signature

When completed: one copy to patient; original copy to Site Investigator File; one copy for medical records. THANK YOU