Protocol: Variation and Determinants of Novel Psychoactive Substance (NPS) Use: Implications for Policy and Practice.
Version 1

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1. **Project title**: Variation and Determinants of Novel Psychoactive Substance (NPS) Use: Implications for Policy and Practice.

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4. **Background:**

The existence of Novel Psychoactive Substances (NPS) is not, in itself, a new phenomenon, however the rate at which these substances have emerged during the past five years is unprecedented. This rapidly changing drug market and the associated harms of NPS are prioritised as areas of concern in regional, national and local drug strategies (ACMD, 2011; EMCDDA & Europol, 2012; FAP Royal College of Psychiatrists, 2014; Home Office, 2012). Collectively, the term NPS refers to a range of recently emerged psychoactive substances which have become popular across several drug scenes in the United Kingdom (UK) and elsewhere in Europe.

The term "NPS" is as broad as the term "psychoactive drug" and encompasses a diverse range of plant-based substances (e.g. salvia divinorum); synthetically produced drugs derived from cannabinoids (e.g. Spice); cathinones (e.g. mephedrone); and piperazines (e.g. BZP) (Winstock & Wilkins, 2011). Initially dubbed "legal highs", these substances often fall outside of existing drug legislation and thus, are, or were previously, legal to supply or consume providing the product is/was marketed as "not fit for human consumption". Governments in most European countries initially responded reactively by implementing early-warning systems to monitor NPS emergence and controlling a number of highly publicised NPS, e.g. mephedrone and synthetic cannabis/spice, through amendments to existing drug law. However, the synthetic production of NPS often means that changing one compound in the chemical composition is sufficient to once again bypass existing law. Thus, NPS manufacture and control has been described as a game of “cat and mouse”. In a bid to intervene, UK policymakers have followed suit with the Republic of Ireland by endeavoring to disrupt the market by prohibiting the distribution of NPS, thus targeting suppliers as opposed to possession.

Prevalence data on NPS use are limited. Their recent emergence as a substantial issue means that, questions on NPS use were not included in general population surveys until the past few years. Furthermore, specific NPS featured in household surveys tend to be limited to those which are highly publicised and of most interest to policy makers at the time that the survey is prepared or issued, e.g. mephedrone (Sumnall et al., 2013). For example, following their prohibition in 2009, questions on BZP, GHB and Spice were included in the British Crime Survey (BCS) and mephedrone was added to the list in 2011. Data from the BCS (2010-11) show use of BZP, GHB and Spice in 2011 as extremely low among young adults (16-24 years) (0.2%; 0.1%; 0.4% respectively). Mephedrone was one of the more popular NPS, with use estimated at 4.4% among young adults, comparable to powder cocaine (Sumnall et al., 2013). Prevalence surveys from Ireland, North and South, feature questions on a wider range of NPS than the BCS. The NI Drug Prevalence Survey in 2010/2011 dedicated an independent section to mephedrone, undoubtedly due to the high level of media attention and public concern regarding the emergence of the drug. Lifetime use of mephedrone among 15-34 year olds in Northern Ireland was estimated at 2%.

To date, little is known about patterns of NPS use and associated harms (ACMD, 2011). More recent studies have focused singularly on some of the more established NPS, such as BZP and mephedrone. The study in this proposal is unique in that it will not focus solely on one particular NPS, or on any single group defined by their pharmacological properties (such as stimulants, hallucinogens etc.).

A review of research on BZP as a recreational drug (Cohen and Butler, 2011) highlighted potential health risks associated with use, including headaches, tremors and poor concentration (Wilkins et al., 2006). Similarly, a systematic review of empirical research on mephedrone (Brennan and Van Hout, 2012) identified several health concerns associated with use of the drug, particularly around toxicity, compulsive use and adverse side effects, including sore nasal passages, hot flushes, loss of appetite, nausea and insomnia (ACMD, 2010; Dargan et al., 2010; Deluca et al., 2009; EMCDDA, 2011; James et al., 2011; Winstock et al., 2011; Wood and Dargan, 2012). Furthermore, there is still considerable uncertainty around the long-term effects of different types of NPS and existing knowledge is based on a

range of sources on different levels of reliability, including hospital admission records and information posted through online drug forums.

There are few published studies relating to the dependence and abuse potential of mephedrone and other well established NPS (Wood and Dargan, 2013). Anecdotal evidence suggests dependence-like symptoms associated with use of mephedrone and an increase in referrals to some drug services, particularly in Northern Ireland, have been linked to increased use of the substance in the region (EMCDDA).

NPS are treated very much in the same way as illicit drugs in terms of control and treatment; i.e., through policing channels for control and referrals to existing drug agencies and outreach teams for treatment. In the midst of the unknown, it would appear that policy makers and practitioners have assumed a "one size fits all" position and assumed that NPS use can be managed in terms of harm reduction, treatment etc. in the same way as traditional illicit drug use. This might be premature, given that the assumption is unsubstantiated and potentially opens the floodgates to harm as the market for NPS continues to grow. This study will address this uncertainty directly by making a comparison between patterns of NPS use and the use of traditional substances and associated harms. It will determine the transferability of information on these traditional substances to policy and practice for NPS.

5. Risks and benefits

Secondary analysis of the Belfast Youth Development Study data will place no additional burden on participants, since the data have already been collected and robust, tested procedures are in place to protect their confidentiality. The team is experienced in using Belfast Youth Development Study (BYDS) data and are capable of ensuring that none of the research outputs could allow the potential identification of individuals or participating schools.

In relation to the gathering of new data, we will be sensitive to the fact that BYDS participants are being re-contacted to take part in further research. We will pay attention to issues surrounding respondent burden and develop protocols for the recounting of historical responses to questionnaires. Recruitment protocols will be designed to ensure we do not jeopardise participation in future BYDS sweeps. For the qualitative component of the study, there is always the risk that uptake from the BYDS cohort could be low but we have mitigated against this by including a supplementary sampling framework outside of that population. More generally, there are risks involved with collecting data from any population which may be considered vulnerable, including substance users. Participants in the narrative interviews will be assured that all data will be confidential within the confines of standard ethical procedures. However, the rapid rate at which NPS emerge and are controlled by law blurs boundaries around licit and illicit substance use. Protocols will be put in place to ensure the safety of all interview participants and the research team. Should respondents display signs of problem NPS use, they will be signposted to relevant services. The wellbeing of research participants is paramount and if a participant becomes distressed during the interview, data collection will be terminated.

The knowledge exchange groups will consist of healthcare professionals, practitioners, academics, service providers, and service users, i.e., NPS users. We anticipate that this involvement will pose minimal risk to all members of the knowledge exchange group with the possible exception of NPS users and the protocol for this will be similar to that described above for narrative interviews in order to protect confidentiality and avoid distress. In terms of burden for those participating in the knowledge exchange sessions, the research team will ensure that meetings are held at a time and venue convenient for members of that group. Each group will be bound by data confidentiality during exchanges in which personal experiences are shared.

The benefits of participating in the study are perceived to outweigh any possible risks. The research has the potential to be transformative through the development of a fluid and transferable framework of best practice that will be geographically transferable to those working in the field of NPS. The longer term benefits to NPS users of the production of such a framework will be the possible impact on NPS service delivery, including treatment services for NPS users, as well as education and prevention initiatives UK wide.

6. Rationale for current study:

NPS are emerging at an unprecedented rate; in 2012 the number of NPS available globally (n=251) exceeded the total number of substances under international control (n=234) (UNODC, 2013) and by 2014, it was estimated there were more than 350 NPS on the market. Prevalence data suggests these substances have become firmly embedded in UK drug scenes (FAP Royal College of Psychiatrists, 2014). To date, research around NPS, including pathways into use, trajectories and patterns of use and associated harms is exceptionally limited, thus, evidence based policy and practice is virtually non-existent. The ministerial review of NPS recommends commissioned research in these key areas.

7. Research objectives:

This study aims to examine the use of NPS within a conceptual framework, which elucidates the harms of use. It will provide information to inform future practice around the prevention, harm reduction and treatment of NPS use.

Research questions include:

1. What are the types and patterns of NPS use including the quantity and frequency of consumption, setting of use as well as sources of obtaining the drug?

2. What are the developmental pathways into NPS use and are these similar or different for specific types of NPS (stimulant type NPS, hallucinogens and depressants or downers)?

3. Is there an association between NPS use and health and social outcomes (e.g. mental health, educational attainment, employment status etc)?

4. What are the patterns of NPS use as they relate to other substance use?

5. Why do individuals with similar socio-demographic profiles and illicit substance use differ in their decision to use or not use NPS? What are the emerging factors that contribute to this decision to use or not use NPS?

6. Does the drug taking profile of an NPS user differ according to age, gender, social class and across differing traditional drug using groups?

7. What are the associated harms with NPS use and how are these similar or different to that of traditional illicit substances?

8. What are the appeals of NPS and how are these similar or different to those of traditional illicit substances?

9. What are the risks associated with NPS use and how are these similar or different to that of traditional illicit substances?

10 What knowledge and/or experiences do NPS users have of treatment services for NPS and how is this similar or different to knowledge and/or experience of services for other substances (licit and illicit)?

11. How can the research findings be integrated into a framework to inform existing service provision, policy formation, and educational initiatives UK wide?

8. Research design:

Fundamental to the design of the proposed research is the blending of a high quality longitudinal data set with in-depth qualitative inquiry which together allows comprehensive and comparative description of the pathways to use and non use, as well as carefully considering the potential harm and public health burden of NPS use. NPS are categorised broadly to include stimulants, hallucinogens and downers/depressants. Using high quality evidence from an established longitudinal study complimented by contemporary qualitative enquiry, the research seeks to develop a working model which has utility for those responding to the recently articulated challenges posed by NPS use in policy and practice communities across many contexts. The study design supports the principles of methodological eclecticism, that being the most appropriate techniques have been selected from a myriad of both qualitative and quantitative approaches to comprehensively investigate NPS use. Accordingly, the study design has been configured to best address the defined research questions.

Quantitative analysis will exploit Belfast Youth Development Study data examining patterns and outcomes of NPS use, categorised as above. The BYDS is a longitudinal study of the onset and desistance of drug use among young people in Northern Ireland and is described in detail elsewhere (see Percy, A., McCrystal, P. & Higgins, K. (2008). Around 5,000 young

people attending over 40 schools and non-mainstream education programmes took part in the study. The first sweep was in the year 2000, and all pupils in their first year of post-primary education in participating schools were invited to take part. This cohort of pupils was surveyed in each successive year for the five years of compulsory schooling, and again in the 6th year whether attending school or not. Then, in 2010/2011, sweep 7 used an online survey or paper survey delivered to their home address by fieldworkers to gather the most recent data. In that sweep, information on mephedrone and questions on use of legal highs (open ended question) were included for the first time. This information will be scrutinised in this study to uncover information on the types of NPS used, patterns of consumption, including quantity, frequency and settings of NPS use, as well as sources of obtaining the drug. A key strength is that concurrent health-related and other behaviours will also be examined to provide a comprehensive understanding of NPS use in context. This may include poly drug use, anti-social behaviour, contact with the criminal justice system, education, self-harm and mental health outcomes. Analysis will use approaches including Latent Class Analysis (LCA) and multinomial regression models to assess the predictors of NPS consumption patterns, multilevel models to assess school and area variations, and further regression models to assess associations between NPS use patterns and health and social outcomes including harms. Specifically, LCA will estimate the number and nature of classes, in order to determine (1) if there are meaningful sub-groups within the NPS population in terms of consumption patterns/risk and (2) if the classes differ qualitatively or quantitatively in terms of pathways into substance use, and in terms of outcomes.

This study will use a nested case-control design with cohort data from sweep 7 of the BYDS. This design is well suited to the objectives of this study, which seek to identify possible predictors of outcome. In addition, given the rapidly evolving nature of NPS and the differential outcomes, this is appropriate, and often used, to generate hypotheses that can then be studied via prospective cohort or other studies. In undertaking the secondary data analysis, we will primarily identify and construct cases and controls to attain an NPS-use group and a non-NPS use group. The groups will be matched on key variables including age, gender and demographics. In order to disentangle the characteristics that significantly predict NPS use and non-NPS use, we perform logistic regressions to assess the impact of a number of key factors on the likelihood of use. These will include, for example, age, gender, affluence, psychosis score and depression score. This will inform the second stage of our analytic plan where we will apply Latent Class Analysis (LCA) to address how the identified indicators cluster across individuals. LCA is particularly well suited to the aims of this study. Firstly, it is exploratory in nature, which is important in this rapidly evolving field, and it is primarily data-driven, meaning that a priori assumptions are not made concerning the number of latent classes present. However, based upon the extant empirical literature, we know that there are likely to be configurations that will contribute to the differing outcomes. We will use six characteristics to identify latent subgroups: mental health (Vergara-Moragues et al., 2014), education (Langford et al., 2014), employment (Compton et al., 2014) involvement with criminal justice system (Gordon et al., 2014), socioeconomic status (Kendler et al., 2014) and traditional drug use. Secondly, LCA will facilitate the inclusion of multiple measures of risk/harm without assuming independence among the indicators. This will allow us to describe and explain both usage patterns and trajectories of use. A major advantage of the use of LCA in this study is that it assigns individuals to classes on a probabilistic basis, allowing comparison of rates of NPS use and other correlates across

classes. In the next phase of the research, we will theoretically sample participants from the identified clusters and invite them to take part in qualitative narrative interviews to explore NPS use and its implications in more detail. This will provide a unique opportunity to integrate quantitative material with qualitative information, in order to explore and cross validate emerging outcomes. By modeling unobserved population heterogeneity, mixture modeling provides new insight in important areas of drug use, such as helping to identify at-risk individuals and examining intervention impact on subgroups characterized by different drug use patterns or different types of growth trajectories of drug use practices. The profiling of NPS consumption and usage patterns using multiple identifiers has notable analytic and conceptual benefits, and, in combination with the qualitative aspect of the current study this particular analytic strategy has the potential to elucidate information on other key issues such as desistence and the effects of maturation and perceived risk. This mixed methods approach offers an especially promising path toward using research design in ways that support rigorous inquiry. In particular, linking statistical analyses to qualitative knowledge can strengthen causal inference. Scientific progress depends on refuting conventional ideas if they are wrong, developing new ideas that are better, and testing the new ideas as well as the old ones. Qualitative evidence can play a key role in all three tasks and one of the substantial strengths of this study is the integration of the different methodologies to apply a rigorous approach to resolving uncertainties about NPS, in an area which is challenging for research as well as for society. A key point here is that the approaches we will take can add inferential leverage that is often lacking in quantitative analysis (Collier, 2011). The strengths of the iterative research design whereby quantitative and qualitative components feed into one another, coupled with input from the knowledge exchange group, will ensure that study findings contribute to a robust, geographically transferable and future proof model of best practice for those working in the field of NPS. We are not aware of any previous published work that has applied such an approach, but have assembled a multi-disciplinary team that is capable of implementing this comprehensive design. With this in mind, we envisage the quick production of a number of interim reports and findings, as the study progresses.

In the first instance, qualitative data will be gathered through the collection of retrospective narratives from NPS users (lifetime use) in the BYDS cohort. We will theoretically sample participants and a control group of non-NPS users, matched on the key characteristics that significantly emerge from the preliminary logistic regression analyses (see section 15 statistical analysis). This sampling framework will ensure that we gain as wide a range of perspectives as possible. Using the BYDS analysis, we will also be in a position to highlight areas worthy of additional or more concentrated enquiry. Based on this, we will further supplement the qualitative component of this study to ensure we capture a wide age range, an up-to-date contemporary outlook, additional geographical locations, various configurations of use and, in keeping with an inductive design, any other emergent perspective central to our pursuit of a comprehensive analysis of the issues. In order to maximise the chances of achieving wide ranging perspectives, these additional participants will be recruited through a variety of methods which in combination are likely to provide a broad based sample of NPS user. They include (1) a rolling cohort of current NPS users from a study originally conducted on mephedrone use (McElrath & O'Neill, 2010); (2) snowballing from the BYDS sample; (3) through gatekeeper members of the knowledge exchange group (i.e. service users and service providers). In so doing, we will be well placed to provide a

comparative analysis of the harms of NPS across a wider group of participants and examine how the patterns of use may change rapidly over short periods of time. Concomitantly, the study will consider how drug taking behaviour and effects may differ according to age, gender, social class and use within specific peer groups. This sampling framework will enable us to look at the broadest spectrum of NPS use in a contemporary setting. Retrospective narrative interviews with all participants will explore their drug use career, if any, and factors relating to drug initiation or non-initiation (e.g. peer and family influence, education, employment etc) and decision making. Narratives will provide novel data on critical incidents, perceptions of risk, the basis upon which these are founded, and actual harm. Interviews with NPS users will shed further light on the patterns of NPS use, the types of NPS consumed, effects of NPS (e.g. physical effects of NPS in terms of hallucinogenic, stimulant etc as well as experience of different brands and poly consumption), and the availability and accessibility of NPS. This qualitative component will validate our interpretation of quantitative findings whilst enabling us to address some of the limitations of the secondary analysis. Re-contacting the BYDS sample will provide a unique opportunity to investigate trajectories and patterns of use, perceived and actual harm of NPS use (e.g. hospital admissions) and pathways to desistance.

At project inception, a series of knowledge exchange (KE) groupings will be established comprising healthcare professionals, practitioners, academics, service providers, and service users, i.e., NPS users. The knowledge exchange activity surrounding this research comes with the aim of sparking connections between the various components of this research with the wealth of practice expertise brought by the alignment of participants in the group. To overcome the power dynamics (Hardy 2004) we will initially run the various constituent groupings as parallel contributions using a modified Dephi method. Ongoing questions will be posed using the research findings as they emerge further refined by each of the groups responses to produce as cohesive an answer as possible to the emergent challenges and to draft a multi-faceted framework. This framework/model will assist those in practice and policy roles challenged by the fast paced and frequently changing NPS landscape. Taking into account recent legislative change, based on the ministerial review of NPS,(September, 2014), ultimately, it is hoped that the research will lead to the development of a conceptual framework which will provide a common language and approach that is not location specific. The model is likely to be a unique combination of the commonly used four stage person-centred approach to NPS across the lifecourse (Graham et al, 2003; Musselman & Hampton, 2014) overlaid with our empirical findings. The stages are not viewed as discreet or incremental and there may be movement between stages for individuals, whilst others may need help at multiple stages, for example intervention, support and subsequent recovery.

The four stages of the envisioned framework are;

1. Information, education and prevention
2. Advice and harm reduction
3. Intervention and support
4. Recovery and support

The conceptualisation of an adaptable approach, that considers a tri-partite categorisation of NPS within different stages of education, prevention and care, will facilitate a holistic

model of intervention whilst informing multi – disciplinary policy and practice guidance. Such a framework will be shaped by and representative of contemporary NPS, as well as robust enough for geographical transferability and future-proof to cater to changes in NPS markets, use and harms.

9. Study population:

The study population for the quantitative component comprises participants in an ongoing longitudinal study. Members of the study were recruited from post primary schools, and education other than at school projects, in Belfast, Downpatrick and Ballymena. Over 80% of schools in these areas participated in the study. BYDS participants were males and females, aged 21 and 22 years, at the time of data collection in 2010. The qualitative BYDS sample will now be 25 and 26 years of age. Supplementary recruitment will yield males and females from a broad age spectrum. Participants recruited from the mephedrone study (2010) will now be between 23 and 53 years of age. Participants will also be recruited through both adult and youth (16 years old and above) services and though snowballing from the BYDS cohort. This sampling framework will capture the diversity of patterns of NPS use which we anticipate will range from experimental to problematic.

10. Socioeconomic position and inequalities:

The Belfast Youth Development Study was a school based survey; the schools and education other than at school projects that took part in the study drew pupils from the full spectrum of affluent and deprived backgrounds, as measured by area of residence (Northern Ireland Multiple Deprivation Measures), and using indicators from the Family Affluence Scale, and free school meal eligibility. In the later years of the study, a range of affluence indicators were collected e.g. information on educational attainment, employment status and occupation.

This study is in a unique position to contribute to the understanding of health inequalities in relation to NPS use. Firstly, by assessing whether NPS use is socially patterned in a similar or different way from traditional substances; secondly, by assessing whether rates of harm are greater among less affluent groups.

11. Methods (Brief explanation):

The main methods are:

(1) Secondary analysis of an existing longitudinal data set.

(2) Narrative interviews (with NPS users and control sample).

(3) Model generation/framework for policy and practice led by the knowledge exchange group.

12. **Proposed outcome measures:**

Available measures in the BYDS include: Psychosis Screening Questionnaire (PSQ); Depression scale of the Patient Health Questionnaire (PHQ-9); Self Harm behaviour (Cf. Hawton); Use of medication; Use of mental health services. Alcohol Use Disorders Identification Test (AUDIT), Drug Abuse Screening Test (DAST); Cannabis Abuse Screening Test (CAST); Offending behaviour and contact with criminal justice system; Educational achievement; Employment status and material well being.

13. **Assessment and follow up:**

We will follow up the BYDS sample qualitatively and collect narrative interviews with NPS users and matched control group. A quantitative follow up is not necessary for the proposed study, but there are plans for a further sweep of the BYDS cohort which will collect another round of such data.

14. **Proposed sample size**:

There were 2,074 respondents in sweep 7 of the BYDS, representing 50% of those eligible to participate (i.e. excluding deceased, refused and booster sample respondents not followed longitudinally), and 35% of the full study cohort. The constraints of this response, i.e. restricted word count, eradicates the inclusion of a more holistic description of the BYDS study and population, however, further information is available from BYDS publications, or upon request.

Of the 2,074 BYDS respondents, a total of 213 (10%) reported the use of some type of NPS. [1]This represents a fair sample size for the study of trajectories to use of NPS (key determinants and risk factors), and can provide indicative findings in terms of patterns and typologies of NPS use.

With a sample size of 2,074 and accepting a type 2 / type 1 error rate of 4:1 (i.e. a much more conservative test and lower risk of false positives), an effect size of 0.06 could be detected with 78% power and type 1 error of 0.053 (Calculations using G*power 3.1.5).

A theoretical sampling strategy will be adopted for the qualitative component of the study using a framework derived from the BYDS analysis. Sampling decisions cannot be determined prospectively from the outset of the study. Sampling, data collection and data

[1] In total, there were 185 mephedrone users and 55 other NPS users (of which 27 had also used mephedrone).

analysis are concurrent activities, with sampling decisions driven by emergent analysis. Sampling will end when the point of theoretical saturation is reached. Theoretical saturation "refers to the point at which gathering more data about a theoretical category reveals no new properties nor yields any further theoretical insights about the emerging theory." (Charmaz, 2006: 189). We anticipate that the qualitative sample will not exceed 70 participants, but equally, if data saturation occurs after 30 interviews, sampling will cease.

Due to the very recent emergence of NPS, there exists a dearth in research and theory, resulting in little/no direction when pre-empting core themes for qualitative analysis. This paucity of existing work encourages a very inductive approach to data collection and analysis, which has the advantage of potentially generating new theory but requires added effort in gaining saturation, in comparison with studies on alcohol, tobacco and some of the more established traditional street drugs. In her research into NPS use among "recreational" drug users in Northern Ireland, O'Neill (2012) reported gaining saturation after 45 interviews, having purposively targeted a convenience sample of drug users and then theoretically sampled on urban/rural residence and known use of NPS. This sampling strategy did not encompass non NPS users or those receiving treatment. The diversity of the proposed sample suggests potential need for more participants, i.e., more than 45.

15. Statistical analysis:

Descriptive statistics and univariate tests will be used to describe the variation and determinants of NPS use. Primarily chi square tests, as NPS use will most often be a binary variable (ever Yes/No, last year Yes/No). These tests will determine whether NPS use varies according to individual (e.g. gender), family (e.g. single parent families), school (e.g. proportion of alcohol/drug users in school) and area (e.g. deprivation indices) characteristics. Descriptive and univariate tests will be conducted on NPS users to describe the variation and determinants of NPS use, to uncover information on the types of NPS used, patterns of consumption and whether NPS use varies according to individual, family, school and area characteristics (e.g. chi-square tests, t-tests, ANCOVAS, regressions (N=213) (e.g. t-tests to compute achieved power indicated for a two-tailed test with an α of 0.05, effect size of 0.05, and a total sample size of 213 this was sufficient to produce power ($1-\beta$) of 0.99.

They will also determine the association between NPS use and levels of educational attainment, mental health problems, and employment status. Multilevel Logistic regression models, with pupil at level 1 and school at level 2, will assess the independent effect of predictor variables conditioning on confounding variables. Directed Acyclic Graphs will inform the choice of 'conditioning' variables. Latent variable modelling approaches e.g. Latent Class Analysis will be used to identify if there are discrete groupings of drug & NPS users. For example; traditional smoking drugs only, traditional and novel smoking drugs, traditional and novel stimulants and smoking drugs, alcohol and tobacco only etc. Latent Class Analysis (LCA) will be applied to the entire data set (N=2074) to identify the number and nature of classes based on a range of items measuring drug use patterns which will increase the power to detect meaningful classes. We hypothesise that a NPS class (among others) will emerge alongside a larger class comprising of non-drug users which will be used

in further analyses as a reference/ baseline class and as a framework for our theoretical sampling strategy. As LCA identifies unobservable subgroups within a population traditional power analysis cannot be primarily conducted and depends on nuanced technical choices about indicator definitions and construction. These cannot be fully specified in advance of performing the secondary data analyses. So assessment of statistical power will have to be an iterative process.

Multinomial logistic regression models with NPS user latent class as the outcome will assess which demographic, health, substance use behaviour, family, and school level influences occurring between the ages of 11 and 17 are associated with subsequent NPS use. Logistic regression models with mental health, employment status and educational attainment as the outcomes will assess the association between NPS use and these health and social outcomes, controlling for other individual, family and substance use influences. Multilevel models will be used to account for the clustering of individuals within schools (McCann et al, 2014) Interaction terms will be used to assess the extent to which affluence or deprivation modifies the association between NPS use and health & social outcomes. Particular attention will be paid to issues of reverse causality in relation to education and employment status (themselves socio-economic indicators). The availability of area and family affluence measures from age 11 will greatly assist in the analysis of inequalities. Due to the rate of attrition in the later years of the BYDS study, we will employ multiple imputation methods to account for missing information. We can reason, a priori that those with missing information in the later years of the study are more likely to be heavy substance users. As we have such rich information on their substance use at younger ages, and thus are able to predict the reason for missingness with some accuracy, we can make an assumption that data is Missing at Random (MAR) and estimates should be unbiased. We will conduct extensive sensitivity analyses to assess the extent to which our results change if the MAR assumption is incorrect e.g. by adjusting imputed dataset estimates for NPS use to 5%, 10%, 20% etc. upwards above that predicted by the imputation model. G-Power post hoc z-tests to compute achieved power were performed specifying for a two-tailed logistic regression with an α of 0.05, odds ratio of 1.21 and a total sample size of 2094 this was sufficient to produce power ($1-\beta$) of 0.93. Further the G-Power test specified that for a two-tailed logistic regression with an α of 0.05, odds ratio of 1.6 and a total sample size of 213 this was sufficient to produce power ($1-\beta$) of 0.85. We would expect the power to vary due to clustering by school level for some outcomes but we cannot assess this in advance of doing the analysis (Snijders, 2005)

Stata 13 and Mplus 7 will be used for analyses.

16. Ethical arrangements:

Ethical approval for the quantitative component of the study will be sought from the Research Ethics Committee at Queen's University, Belfast. The BYDS data began before there was a local research ethics committee from which to gain approval, but it has subsequently gained a favourable opinion from the School Committee. An application will

be submitted to the Office for Research Ethics Committee Northern Ireland (ORECNI) for the qualitative component which will involve contact with users of statutory services.

Information about the study

We will develop study information sheets, clearly outlining details of the research, what we are asking from participants, how the data will be used, contact details for the research team and potential risks and benefits of participating in the research. Respondents will be assured that they can withdraw from the study at any stage without their rights being affected.

Free and informed consent

Due to the nature of the research and the requirements of informed consent, the study will only include individuals aged 16 years or above. Study participants will be asked to confirm they have been given free and informed consent prior to participating in the research. At the beginning of each interview, interviewees will be given time to read the study information again and have any questions answered. Consent to participate in the qualitative interviews will be recorded verbally and/or by marking an X on a dated consent form. We will not ask interviewees to sign their names, in order to preserve confidentiality and minimise the legal risk posed to respondents (should they disclose use of now controlled NPS e.g. mephedrone). A "cooling off" period will be put in place wherein participants can withdraw interview data if they retrospectively regret participating in the research. This essentially extends the timeframe for obtaining consent.

Anonymity, confidentiality and data storage

In keeping with Research Governance, all gathered data will be kept strictly confidential. The procedure for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998 and with Queen's University Belfast Data Protection Policy. All members of the team are aware and will fully comply with the law as specified by the Data Protection Act (1998).

Confidentiality and disclosure risk are controlled through the application of information security and data handling policies contained in relevant system level security policies (SLSP). All participants will be informed about the confidentiality of the study and the way in which data will be stored. All data will be pseudonymised and participants' confidentiality maintained throughout. Participants will be allocated a unique identifier which will be used to identify all paper and electronic records. Only the research team will have access to this.

The research team will be responsible for maintaining separate, confidential registers which contain the participants' unique identifiers. These will be stored securely and separately from other data, with access limited to designated persons. Research will not be conducted on identifiable data.

Raw data will be stored securely in encrypted electronic files or in a locked cabinet and destroyed after a period of three years. Consent forms will be stored separately in a secure cabinet and will not be attached to individual interviews or instruments. Audio recordings will be used for transcripts for interviews and as a 'back-up' if consent needs to be checked. Permission will be sought for this in advance. The audio data will be stored electronically in

an encrypted file and the digital recordings destroyed immediately after the completion of the report. The research team will use computers that are password protected.

Safety and wellbeing of participants

The safety and wellbeing of study participants and researchers is a priority. As mentioned previously, study participants will be made aware of all potential benefits and risks prior to participating in the research. A risk assessment will be undertaken to identify and mitigate against potentially adverse effects of the research. For those participating in interviews, regional information to signpost individuals towards relevant services for problem NPS use/advice will be provided.

17. Research governance and management:

The research will be sponsored by Queen's University, Belfast and led by Kathryn Higgins who has a wealth of strategic and operational management experience, including the leadership of multidisciplinary research teams within the University sector. She has co-ordinated the work of geographically dispersed work teams, and is used to managing budgets in excess of the funding currently requested.

Management

The Management Group (MG), Mc Cann, O' Hara, O'Neill (N), Higgins, Campbell and O'Neill (T) will work with Clarke and O'Neill (F) to assure the delivery of the work programme, to time and to a high scientific quality. A Memorandum of Understanding, based on the final work programme, will be drawn up at commencement with clear protocols covering: governance and accountability, programme of activities, collaborators roles and their relationships to the MG, the planning and delivery of outputs, and the commitment of resources. A strategic plan for maximising impact will also be developed from the outset in accordance with the Knowledge Exchange Groups. The MG will meet bi-monthly, with more regular meetings among smaller staff groups (e.g. those responsible for quantitative and qualitative components). The group will review reports from each of the research components, will identify any problems and ensure their resolution. Staff will develop risk registers for delivery of work on each component of the research. Workshops involving other team members (including additional members of the BYDS team) will be organised to coincide with upcoming MG meetings, in order to enhance skills in interdisciplinary, and develop capacity among staff.

Knowledge Exchange Activity & Groupings

An important strength of the proposed study is that it uses longitudinal data analysis and primary qualitative data in combination with a dynamic knowledge exchange component with limited extra cost. This configuration offers the best potential to help address the contemporary challenges in responding to NPS use to push out research and a suggested framework to inform and support promising practice in this area. The team and all collaborating partners are very experienced in working with key stakeholders, including policy makers, practitioners and drug user advocates, both as members of the public and as users of services. The knowledge exchange activity surrounding this research comes with the aim of sparking connections between the various components of this research with the

wealth of practice expertise brought by the alignment of participants in the group. To overcome the power dynamics (Hardy 2004) we will initially run the various constituent groupings as parallel contributions using a modified Dephi method. Ongoing questions will be posed using the research findings as they emerge further refined by each groupings responses to produce as cohesive an answer as possible to the emergent challenges and to draft the framework to assist practice.

The collective Knowledge Exchange Groupings will be comprised of key individuals from government, statutory sectors, community sectors and academia as well as service users and will in some configuration meet formally 4 times over the course of the project. These groupings will correspond and meet on a more frequent and responsive mode basis particularly as the project progresses to conclusion. We have agreement for participation from of a wide range of service provider organizations, professional groupings and sectors.

18. **Project timetable and milestones:**

	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17
Project startup meeting																	
1. Obtaining ethical approval																	
Develop ethics applications for QUB (secondary data analysis)																	
Develop ethics application for ORECNI (primary research)																	
Obtain ethical approval and global governance																	
2. Knowledge exchange groups																	
Establish and make contact with members of knowledge exchange groups																	
Initial meeting of KE groups to discuss BYDS analysis and qualitative component																	
KE group meeting to discuss qualitative data collection and additional/ ancillary BYDS analysis																	
KE meeting to discuss analysis of findings to generate framework for policy and practice																	
KE meeting to discuss final report and interpretation of findings. Finalise plans for dissemination																	
3. Secondary data analysis																	
Data extraction plan prepared and finalised																	
Consultation with KE groups re: data analysis																	
Secondary data analysis ongoing																	
3. Qualitative interviews with NPS users																	
Fieldwork documentation developed e.g. information sheets, interview schedules etc.																	
Discussion of interview schedule and recruitment plan with KE groups - revise accordingly																	
Participant recruitment to study (BYDS participants)																	
Recruitment of non-BYDS participants (if required)																	
Conduct narrative interviews with NPS and non-NPS users																	
Analysis of qualitative data																	
4. Reports and outputs																	
Preparation of final report																	
Final report discussed with KE groups and finalised.																	
Preparation of papers for peer review																	
Dissemination of outputs																	

19. **Expertise:**

Dr Kathryn Higgins has strong background in substance use research, using both qualitative and quantitative methods, and has worked on the BYDS since its inception. Higgins will be responsible for project-management of the research, and quality assurance of interim findings and final outputs.

Dr Nina O'Neill has expertise in ethnographic research with recreational drug users; socio-epidemiological perspectives on drug use; and assessing risk among drug users. O'Neill (N) will convene the knowledge exchange group, with assistance from Higgins, and will collect and analyse qualitative data.

Dr Tara O'Neill is a Research Fellow working at the ICCR and has extensive experience of statistical methodology and its application. O'Neill (T), with assistance from O'Hara, will undertake the secondary analysis of BYDS. Both will liaise with McCann during this phase of the research.

Dr Leeanne O'Hara is a Research Fellow working at the ICCR. O'Hara's primary area of interest is in adolescent substance use. She has expertise in ethnographic research, innovative approaches to data collection, and fieldwork management for randomised trials. O'Hara will coordinate and undertake the secondary analysis of BYDS data with O'Neill (T); assist O'Neill (N) with the collection of qualitative data and liaise with Clarke in the application of methods to the research study.

Dr Anne Campbell has experience in drug and alcohol research using qualitative and quantitative methods. She also has conducted research with young people who have substance abuse problems, both within the general population and within specific young offender populations. Campbell will assist O'Neill (N) and O'Hara in the collection of qualitative data and also liaise with Clarke in the application of methods to the research study. Campbell, O'Hara and O'Neill (N) will also draft documents for the School ethics committee and ORECNI (where appropriate), and will recruit participants onto the study.

Prof Mike Clarke is Director of the MRC All-Ireland Hub for Trials Methodology Research and Chair of Research Methodology, Queen's University Belfast. Clarke has extensive experience in the conduct of prospective research and has research experience in substance misuse. He brings expert knowledge on study design and novel analytical approaches.

Dr Mark McCann is a research fellow at the MRC/CSOP Social and Public Health Sciences Unit, University of Glasgow. He is working as part of the Public Health Intervention Research Methods team, and his fellowship is based on developing methods to integrate causal theory and evidence into service design and planning. He has expertise in the analysis of cohort studies, administrative data, RCTs and service evaluation, and providing training in statistical and epidemiological methods. McCann will advise on the quantitative analysis and assist in preparation of data and undertaking analyses.

Dr Francis (Tony) O'Neill has expertise in psychiatric medicine and substance misuse. O'Neill (T) will contribute as an advisor to the project.

All applicants will contribute to the final report and associated publications, and will assist with dissemination and impact.