The Novel Psychoactive Substances in the UK Project (NPS-UK)

Background

While illegal drug use has, largely, been declining in the UK over the past decade (1), this period has witnessed the emergence of a range of new, mostly synthetic substances that mimic many of the effects of "traditional" drugs. These are known as "legal highs", or new or novel psychoactive substances (NPS). The latter description refers to the fact that use of the substance(s) in question has not been specifically prohibited. The Advisory Council on the Misuse of Drugs (ACMD), the expert body that advises Government on drug policy and practice issues, has defined NPS as: *"psychoactive drugs which are not prohibited by the United Nations Single Convention on Narcotic Drugs or by the Misuse of Drugs Act 1971, and which people in the UK are seeking for intoxicant use*" (2).

NPS use provides a number of grounds for concern. First, technological advances offer sources of supply the capacity for continuous product innovations, leading to rapid increases in the numbers of different substances available, and despite speeding up the legal processes in the UK for controlling these substances (3), the rapidity of the technological developments outstrips legal controls. Second, they are readily and cheaply available through the internet and 'headshop' outlets as well as from traditional drug dealers (4). Third, by international standards, there are very high levels of cultural acceptability of NPS use in the UK (5). Fourth, they are perceived to be safe, or to pose little risk. Fifth, there are large uncertainties surrounding the identity of individual substances purchased online and on the streets. Even when a new substance is clearly and accurately identified, there may be very little information on effects, the risks posed by its use, and how these may be reduced.

Despite such causes for concern, there has been little consideration of the public health burden associated with NPS use, apart from investigations of acute problems presenting to health services, and fatalities (6-9). Also, whilst there has been valuable thinking done about the implications for the regulation of drug use (4, 10), dedicated attention to specifically public health responses has been limited (11). This proposal seeks to address these gaps.

UK general population surveys report past year use prevalence of mephedrone, which has attracted most concern, ranging from 1.1% to 1.8% among those aged 16 and older (12, 13), with prevalence largely stable in more recent years (1). However, among those aged 16-24 years, last year use prevalence has been 3% or higher, similar to that of ecstasy (12, 13). The most recent national drug survey identified increases in the past year prevalence of nitrous oxide and salvia use, in both the younger 16-24 age group, and among all adults. Among the former, past year prevalence was 7.6%, approximately twice that of both ecstasy and powder cocaine (1). Moreover, a number of deaths have been associated with mephedrone use, both before and after it became controlled (14, 15).

Monitoring of the emergence of new drugs through early warning systems, and of national policy responses in Europe, is undertaken by the European Monitoring Centre for Drugs & Drug Addiction (EMCDDA) (16, 17). Very little work has been undertaken, however, on the problems associated with use, with scant consideration of the need to develop interventions that target NPS. This is despite the strong focus on developing the evidence base to support responses to NPS in the UK Drug Strategy (18). These needs have also been emphasised for some years by the ACMD (2).

It is currently unclear how much dedicated targeting of the existing generation of NPS is needed, as the existing data suggest that NPS are rarely used by those who are not also involved in other forms of substance use (12). Even if the present generation of NPS are not very problematic, and it is very unclear whether this is so, there is a need to develop the capacity for public health NPS responses to new substances which may become problematic in the future. The longer term strategic need may be to develop the evidence base in such a way as to be able to identify and intervene early with some new drugs that appear likely to be particularly problematic, and by implication not others, in order to alter the course of possible future epidemics (19).

There is therefore a pressing need to review what is known about NPS use in the UK, the extent and nature of problems associated with this use, and to consider potential public health responses. There have been no systematic reviews which evaluate what is currently known about NPS use in the UK. Moreover, given the continually changing nature of NPS use and the resulting uncertainty regarding their implications for public health and the NHS, it is important that strategic research efforts are not confined to the current generation of NPS, but are capable of adapting to new drugs that should be expected to emerge in the years to come.

Research aims and objectives

The overall aim of this proposal is to inform the development of public health intervention research on NPS through systematically reviewing existing data on their use in the UK, the associated problems and the potential responses. Our three specific objectives are as follows:

1. To summarise and evaluate what is known about NPS use in the UK and related harms and responses through the conduct of a systematic review of peer-reviewed and grey literature.
2. To develop a dedicated conceptual framework for a public health approach to NPS use which identifies the scope for interventions based on approaches developed for the use of other legal and illegal drugs, and the concerns of public health and prevention more broadly.
3. To produce a statement of public health intervention research issues for NPS use in the UK that makes recommendations on key evidence gaps and priorities for future research.

There are two study components corresponding to the first two study objectives, comprising one major study component (in relation to objective 1) and one smaller study component (objective 2). Synergies between the two study components are a key feature of this proposal. The conceptual framework is elaborated in part to assist with the narrative synthesis of the data from the NPS systematic review. It is then used also for the construction of a robust assessment of key evidence gaps and research priorities, and articulation of the key issues facing public health intervention research (objective 3).

Study component 1: NPS systematic review

This systematic review will summarise and evaluate what is known about NPS use in the UK, and on related harms and responses from the international literature. The overarching objective for this study is to identify what is known about NPS use in the UK. In fulfilling this objective, we will endeavour to answer the overarching research question, formulated as “what is known about NPS use, related problems and responses in the UK.”

We develop the research questions that will be answered in relation to the overarching research question in areas defined by the three core concepts of use, problems and responses, and also identify a small number of more methodological questions to be considered. Within these three areas identifiable research questions corresponding to the content of our preliminary conceptual maps are set out below. In each case, we will examine data available to answer the questions, and if the data do not exist or are insufficient, consider to what extent this constitutes an important evidence gap, with evaluation shaped by the conceptual framework.

1) NPS Use

a) What are the prevalence and patterns of NPS use in the UK general population and do they differ in particular subgroups of the population?

- Which are the main NPS being used in the UK general population 2010-2014 inclusive?
- Is there any evidence of changes in NPS use prevalence within the 2010-14 time period?

- Which sub-populations/groups are using which drugs and is there any evidence of change over time?
- What are the patterns of NPS use in frequency and quantities per occasion of each drug?
- How transient, stable or dynamic are patterns of NPS use, and what influences any transitions?

b) *How do existing patterns of both legal and illegal drug use and social and other risk factors influence NPS use?*

- Is there any evidence that those (children, adolescents or adults) who use NPS are more likely to go on to initiate use of illicit drugs (gateway effects)? If so, does any such risk increase with increased involvement of NPS?
- Is there any evidence of drug users switching to NPS which may be less harmful (reverse gateway effects)?
- What are risk factors for initiation of NPS use among different populations (eg school children, clubbers)?
- What evidence is there of social patterning or relationships to health inequalities in prevalence and patterns of NPS use?

c) *Which other population-level risk factors influence NPS use?*

- How available are different types of NPS, and by what means are they accessed?
- How costly are NPS compared to other legal and illegal drugs?

2) *Problems*

a) *Which intoxication problems are associated with NPS use?*

- Which NPS cause the most serious acute/intoxication effects?
- Are there known drug interactions or acute poly drug use complications and what is known about their prevalence?
- How common are these effects for different substances?

b) *What problems are associated with regular NPS use?*

- How long does it take non-intoxication problems to develop after use is initiated?
- Which NPS cause the most severe regular use and dependence problems?
- Which problems are associated with dependence on NPS and what might be acceptable intervention strategies?
- How common are problems?
- Is cessation or reduction in use difficult to achieve if problems are encountered for specific substances?
- How do NPS users seek help?
- What help might those with problems like?

c) *In addition to intoxication, regular use and dependence problems, are there other types of NPS-specific problems or other problems associated with NPS use ?*

- Are there other types of health problems?
- Which social problems are there?

- How well do existing problem classification schemes capture the problems experienced by NPS users?

3) Responses

a) Are there dedicated primary or secondary prevention interventions in the UK, and if so what is known about their outcomes?

b) Which generic interventions (early in life and early in drug using careers) target NPS?

c) How extensively does current generic UK drug prevention practice cover NPS?

- Are there modifications to existing UK practice possible on the basis of international data?

d) How good are treatment outcomes for NPS?

- How do treatment outcomes for NPS in the national treatment system compare with those for other drugs?

e) What promising approaches are currently available, or can be made available, in the UK for intervening with NPS use?

- Do online drug interventions incorporate NPS? If so, is it known whether and how often they are used by UK users?
- Are there other promising interventions being developed or being evaluated elsewhere that may be appropriate for UK study?
- Are there approaches used for other substances, such as brief interventions, that are being considered for development for NPS use and problems?

f) What are the population-level or social structural factors limiting the effects of individual-level interventions?

4) Methodological questions

a) What is the nature of the current early warning systems (EWS) provision?
- Are there any evaluation data on the EWS?
- Which non-EWS epidemiological data are available?
- Which qualitative data apart from those used in EWS are available?
- What do the EWS tell us about possible future trends in use prevalence?

b) Are there sentinel populations capable of being monitored to provide early warnings of new trends?

c) What are the issues raised by uncertainties about the identities of substances being used?

We will undertake this work in two stages as follows:

Stage 1: Evidence mapping

For reviews addressing complex topic areas, evidence mapping is a well established tool to explore relevant literature before progressing to more advanced research design decision making (20).

Protocol development & search strategy

We will develop a PROPERO registered protocol describing methods for evidence mapping and the subsequent synthesis. After Stage 1 evidence mapping is completed, we will update the protocol to refine inclusion criteria and other aspects of the study design for Stage 2. Published literature will be identified from systematic searches of electronic sources, reference checking and contact with experts in the field. The following databases will be searched: MEDLINE, EMBASE, and PsycINFO from January 2005 to June 2015; see below for sample strategy in EMBASE. This was run in October 2014, and all searches will be re-run twice in order to identify studies published until the end of 2015. We will also conduct citation searching of included studies using Google Scholar, Scopus, Web of Science and OVIDSP MEDLINE.

Grey literature will be identified from a variety of sources including experts in the field, national surveys and national monitoring systems in the UK (such as the Crime Survey for England and Wales; Smoking, Drinking and Drug use among Young People in England; other Office of National Statistics publications and the National Drug Treatment Monitoring System). International surveys and data from early warning systems that include the UK, such as ReDNet, will also be identified. In addition, we will search for policy documents applicable to NPS use in the UK through searching websites of relevant organisations (e.g., ACMD, EMCDDA). Preliminary work suggests that searching the grey literature databases is not likely to be efficient. We will examine whether to use any grey literature databases, and if so which, during the initial protocol development phase.

Estimate of the size of the available literature

In searching EMBASE, we identified 4,900 records and estimate that 540 records will provide data on NPS consisting of case reports, detection/surveillance studies, qualitative and quantitative cross-sectional studies. Searching across all databases we estimate identifying approximately 8,000 records, assuming the total number of records will increase by approximately 60% based on previous similar searches. We estimate that approximately 880 of the 8,000 records will be potentially relevant, assuming an 11% hit rate, as identified in the EMBASE search.

Initial screening & study selection

This will be conducted by one researcher and all decisions will be checked by another. Any discrepancies will be resolved by consensus or in discussion with a third researcher. Broadly inclusive selection criteria are as follows: Population - people who use novel psychoactive substances; Study design - no restrictions applied; Other - English language publications only.

Mapping

On the basis of information in the abstract, one researcher will map the literature to study design, principal focus (use, problems, responses), study location and relevance to UK categories and this will be checked by another researcher. These data will provide a comprehensive yet concise descriptive map of the nature and breadth of research on NPS, and identify obvious research gaps. In addition, we will use the evidence map to refine our selection criteria (in consultation with stakeholders) in order to conduct the NPS synthesis addressing questions of primary relevance to the UK, in ways which are manageable within the time and resources allocated to the project.

Stage 2: Synthesis

Full texts will be ordered for all studies potentially meeting the refined inclusion/exclusion criteria. Of approximately 880 relevant records, we estimate ordering 200 full text papers of studies conducted in the UK, or undertaken elsewhere and judged relevant to the UK (particularly those on problems and responses). Study selection will be conducted by one researcher and all decisions will be checked by another, with discrepancies resolved by consensus or by involving a third researcher.

Data extraction & critical appraisal

Data extraction forms will be designed by two researchers, piloted on a small selection of studies and adjusted as necessary. Data extraction will be undertaken by one researcher and all data checked by another, with discrepancies resolved by consensus or recourse to a third researcher if necessary. Where necessary, authors will be contacted for missing or unclear data. Critical appraisal will be conducted by one researcher and checked by another for all included studies. We will use checklists reflecting the breadth of study design and aims of included studies, such as those for prevalence (21) and for qualitative studies (22).

Narrative synthesis

We propose to conduct a narrative synthesis of the included studies following current guidance (23). Although the different stages of the synthesis are described here in a linear way for presentational purposes, in reality this will be an iterative process. We will consider the key study foci in the NPS literature emerging from the evidence mapping in relation to our preliminary conceptual maps for use, problems, and responses (see Figures 1-3). To give one example of how more detailed content will be elaborated in component 2, promotion in Figure 1 impacts upon cultural acceptability of NPS use in general, which in turn is informed by and has implications for knowledge of problems associated with, and perceptions of safety of, particular NPS. Interactions between individual and population level risk factors, and indeed other content in the figures, have not been included as this is merely a preliminary guide designed to provide orientation to the issues. For similar reasons we have avoided making the concept map itself overly complex in other ways, and present social risk factors operating only at the individual level, whereas they clearly do also operate at the population level. We have also chosen not to directly relate the content of the three conceptual maps to each other in this presentation. For example, secondary prevention responses may have distinct objectives according to the stage of involvement in NPS use, and whether and to what extent problems are experienced, and if so, which types of problems.

Using the evolving concept map, we will then develop a preliminary synthesis to organise the findings from included studies and to describe patterns across studies. We will then more analytically investigate relationships in the data, exploring factors that might explain any differences in findings according to methodology (e.g., why the sampling method in a particular study might lead to a substantially different estimate than other studies) and study design, population groups and contexts, and in relation to particular substances. We will separate data from opinion, particularly in relation to responses, but also for use and problems. In these ways, data which are broadly reliable will be distinguished from those which are not. Finally, we will assess the robustness of the synthesis with reference to the critical appraisal of the different types of included studies, as well as undertaking further interrogation of findings from earlier stages of the synthesis.

Study component 2: NPS conceptual framework development

This study component addresses directly what it is that we need to know, with the overarching research question needed to be answered to fulfil objective 2 stated thus: What might be the broad approach, and the key elements, of a strategic evidence-based public health intervention response to NPS use in the UK? We approach this question with an orientation to explore, and apply as may be useful, perspectives gained from public health sciences more broadly and responses to other drugs, both legal and illegal. This involves some high level scrutiny of empirical data (24), sensitive to possible differences between NPS and other drugs. This is not primarily a review of empirical data, however, as we will be conceptually reviewing approaches used for other substances.

This study component is designed to interrogate the nature of thinking about potential public health responses. We endeavour to describe the universe of potentially relevant approaches to NPS, drawing on wider thinking in public health, such as on the social determinants of health and on life course epidemiology (25, 26). We will identify those parts of the public health literature, e.g., non-communicable diseases and mental health, likely to be most informative. This exercise also involves making explicit the empirical and conceptual underpinnings of responses to legal and illegal drugs, and examination of the complementarity of possible constituents of a strategic response.

We will select a small number of seminal texts, e.g. (27-29), and identify broad conceptual influences therein. We will explore how these approaches have been applied to other important and complex public health problems. We will use graphical methods as far as possible, e.g. (30). The basis for the development of this framework lies in the public health approach to prevention as defined by Geoffrey Rose (27). In Box 1 we provide a brief outline of selected features of the public health approach to addictive behaviours, regardless of whether the drug is legal, such as alcohol, or illegal, such as cannabis. There are differences between drugs that should be borne in mind (31).

Box 1: Population perspectives on drug use

One should expect a strong correlation between population prevalence of a risk behaviour, and most forms of related health problems (27). Prevention approaches that successfully manipulate both supply and demand to suppress use will contribute to reductions in levels of problems (32). Whole population approaches seek to move the whole drug use distribution to the left, so that both users on average use less, and rates of non-use are increased. There is also a need to intervene in more targeted ways, with those who are deemed to be high risk, for whom whole population approaches may have limited impact. Interventions are tailored to the nature of the risk in such populations, e.g., needle and syringe schemes for injecting drug users.

In relation to alcohol, Skog's theory of the collectivity of drinking cultures (33) underpins most population-level responses. In line with Rose, this perspective posits that alcohol consumption is approximately normally distributed with marked skew towards the heavier consumption tail of the distribution. There is a close relationship between the mean level of consumption and the proportions who are heavier drinkers, because light and heavier drinkers influence each other (33). Reducing the mean level of consumption via universal prevention is attractive as the primary basis of public health strategy for two reasons (28). Firstly it is the most effective strategy for reducing the overall level of problems because it offers a means of addressing 'the prevention paradox' (34) where most problems are generated by those who are low to medium risk, because they are more numerous, rather than those who are high risk. Secondly, heavy drinkers, including those who are dependent are also impacted by universal prevention measures, as the whole distribution moves to the left.

Empirical evidence demonstrates that universal prevention or whole population approaches such as increasing price, reducing availability and restricting marketing in order to influence the cultural acceptability of heavy drinking and drunkenness are those most likely to be effective in reducing a broad range of public health and societal problems with alcohol (28). Direct empirical tests of the overall theory, including those which evaluate change over time, provide additional support (35), though there are also data which are in conflict with that predicted, particularly on the nature of the relationship between overall drinking levels and specific problems (36). This approach does not imply that other parameters, such as expenditure, are not important to policy responses (37).

We will build on the preliminary conceptual models presented in Figures 1-3. For example, population-level risk can be reframed as the interaction of a range of supply (e.g., price, availability and other market features) and demand (e.g., cultural acceptability, promotion) factors, and these are in turn key determinants of levels of use (29). We will elucidate interactions between, the data identified in our preliminary models, and add new material. Examples a-d are provided as follows:

a) Legal status. This is a key determinant of supply and demand (29) and NPS are likely to share similarities and differences with both legal and illegal drugs. The involvement of large scale enterprises, striving to produce new drugs specifically to avoid existing controls, in cat and mouse relationships with regulatory and law enforcement responses, makes it somewhat distinct (10).

b) *Technological advances*. Developments in the content of NPS themselves, and in methods of their consumption, play important roles in relation to levels and patterns of use and their relationships to problems. New technologies have emerged for the ingestion of other drugs such as nicotine (electronic cigarettes) and cannabis (vaporisers) with direct implications for NPS use.

c) Uncertainties around the composition of NPS. Users are often unsure of the specific substance(s) they are using and are therefore ill-informed about potential side-effects and other aspects of risk. It is likely to be appropriate to develop typologies based on drug type (e.g., synthetic cannabinoids or cathinones) rather than focusing on individual NPS.

d) Intervention targeting. Prevention responses may vary in level of targeting (individual, community, population) and at different stages of drug involvement, e.g., experimentation implies heightened risk of intoxication problems, as well as at different points in the life course. Key challenges lie in better understanding inter-relationships in risk as the potential basis of multi-level interventions (38).

Final report: Summary statement of evidence gaps and research priorities recommendations
The final report will provide a summary statement that is a sufficiently concise to be straightforwardly usable in decision making about strategic research needs in the short to long term contexts. This will provide the range of evidence gaps identified across both study components and offer specific rationales for making recommendations on research priorities. This statement will be supported by a comprehensive final report on both study components.

Health Economics
NPS use is likely to have considerable impacts upon the physical and mental health of users, particularly heavy users, imposing health care costs in the treatment of drug related ill health and drug-related accidents. Drug use is also known to adversely affect economic productivity through sickness absences and premature deaths, and impose costs as a consequence of drug-related crime. Inclusion of health economics expertise within the study team permits consideration of the value of existing information identified in study component 1 quantifying the scale of the problem from a public sector perspective based on estimates of NPS use and problems and their relationships with various categories of cost. .

It is anticipated that there will be limited economic data available directly on NPS, though consideration of effectiveness data can yield parameters which can be informative about the research need for various types of cost-effectiveness data. Combining cost effectiveness models with longer term cost models permits a range of projections of the impacts of prevention, and such work can take advantage of health economic investigations of drug use more broadly (44). Such projections can identify the need for specific types of data to investigate the assumptions made in models and contribute directly to the refinement of the study component 2 conceptual framework in the later stages of the project. This approach is designed to allow consideration of the nature of the potential health economic contribution to the wider public health intervention research agenda.

Socioeconomic position & health inequalities
We will seek to examine at every stage of the project the impacts of socioeconomic position and health inequalities, and the evidence for addressing these inequalities. For example, we will examine the influence of such factors on patterns of use and problems in the NPS systematic review as data permit. We have initially located social risk factors, which include inequalities, in the conceptual map for use, though we recognise the importance of consideration of direct and indirect impacts on problems, and also for responses. Deepening our understanding of the importance of these issues will be attained in study component 2. In so doing, we anticipate being able to include content in this area in our consideration of evidence gaps and priorities for research.

Sample search strategy for NPS systematic review in EMBASE

1 exp designer drug/
2 psychotropic agent/
3 drug abuse/
4 2 and 3
5 designer drug*.ti,ab.
6 legal high*.ti,ab.
7 new drug/
8 7 and 3
9 emerging psychoactive substance*.ti,ab.
10 novel psychoactive substance*.ti,ab.
11 new psychoactive substance*.ti,ab.
12 synthetic legal substance*.ti,ab.
13 (psychotropic agent* adj6 abuse).ti,ab.
14 (new drug* adj6 abuse).ti,ab.
15 research chemical*.ti,ab.
16 party pill*.ti,ab.
17 herbal blend*.ti,ab.
18 club drug*.ti,ab.
19 bath salt*.ti,ab.
20 herbal high*.ti,ab.
21 pond cleaner*.ti,ab.
22 smoking mixture*.ti,ab.
23 herbal incense*.ti,ab.
24 synthetic cathinone*.ti,ab.
25 synthetic cannabinoid*.ti,ab.
26 plant food.ti,ab.
27 gamma hydroxybut*.ti,ab.
28 gamma butyrolact*.ti,ab.
29 cannabimimetic*.ti,ab.
30 benzo fury.ti,ab.
31 naphyrone.ti,ab.
32 black mamba.ti,ab.
33 benzylpiperazine*.ti,ab.
34 methoxetamine.ti,ab.
35 mephedrone.ti,ab.
36 salvia divinorum.ti,ab.
37 plant feeder*.ti,ab.
38 psychotropic substance*.ti,ab.
39 ketamine.ti,ab.
40 drug abuse/
41 36 and 37
42 clockwork orange.ti,ab.
43 exodus damnation.ti,ab.
44 BZP.ti,ab.
45 MPVD.ti,ab.
46 NRG-1.ti,ab.
47 MDAI.ti,ab.
48 benzofury.ti,ab.
49 bromo-dragonfly.ti,ab.
50 25i-NBOMe.ti,ab.
51 1 or 4 or 5 or 6 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52 limit 51 to yr="2005 -Current"

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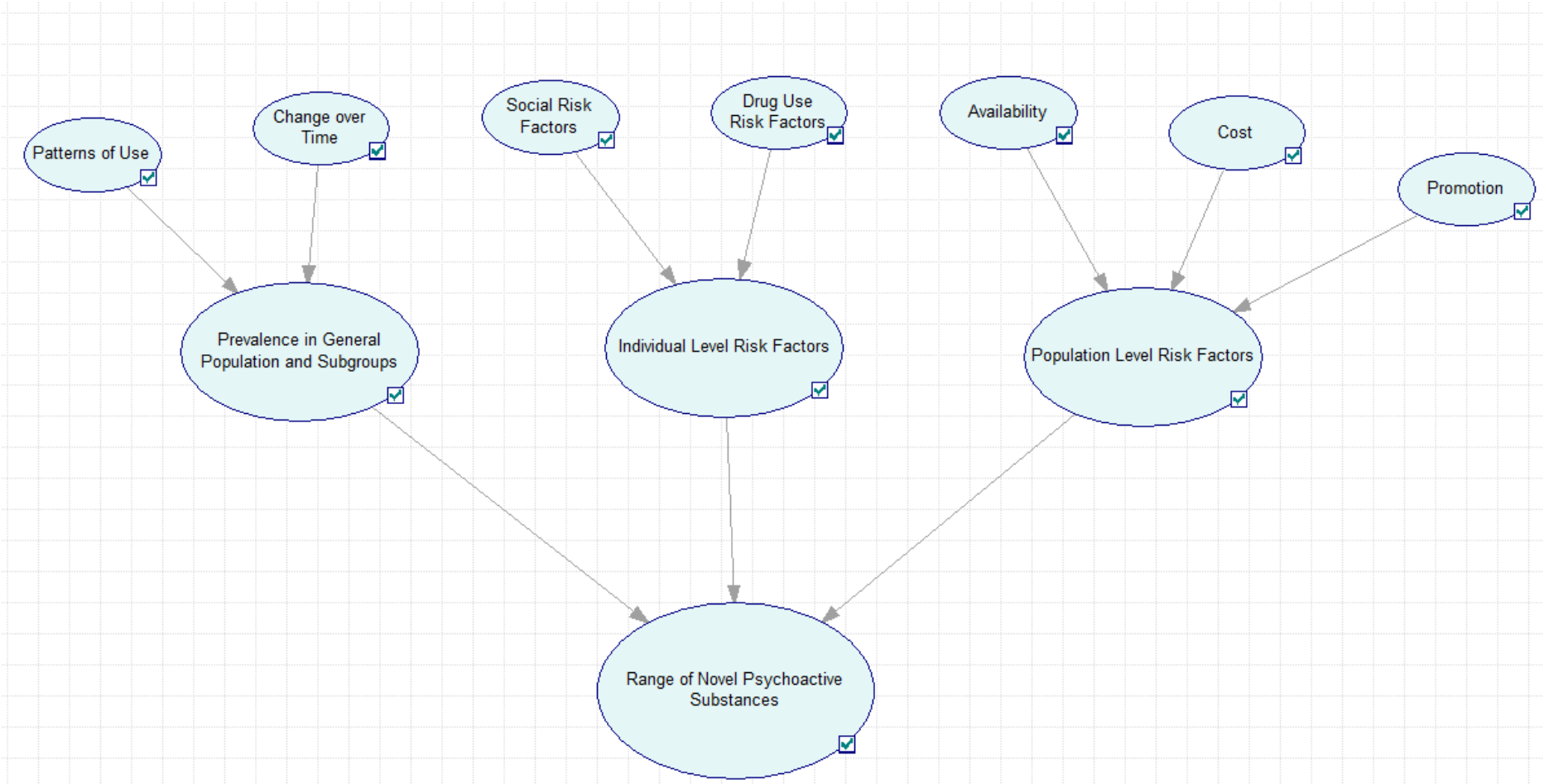
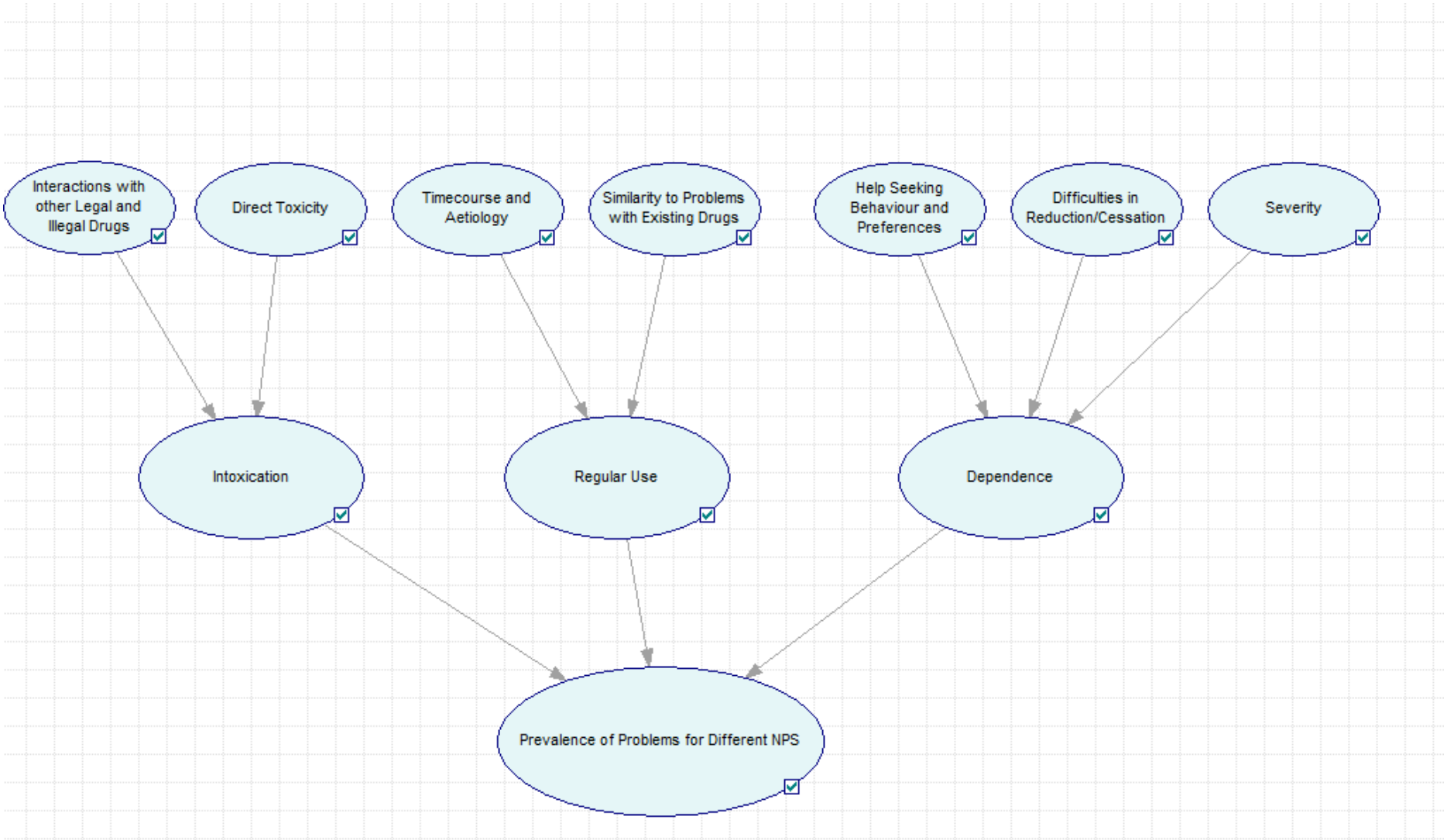
Appendix Figure 1: Preliminary conceptual map of key issues in NPS use



Appendix Figure 2: Preliminary conceptual map of problems associated with NPS use



Appendix Figure 3: Preliminary conceptual map of UK prevention responses to NPS