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)*

NOTICE OF SUBSTANTIAL AMENDMENT

AMENDMENT 1 (V1.0 – 25th April 2016)

BACKGROUND

The IONA study is collecting blood, urine and oral fluid samples from people presenting to UK hospitals with severe toxicity suspected to be related to use of novel psychoactive substances (sometimes called ‘legal highs’). Sample analysis is being performed to identify the substances involved and to link these with clinical features of toxicity experienced by the participant. The study currently involves 11 study sites in England and Wales and 1 site in Scotland (second site in set-up). Because the study can involve adults with incapacity, separate ethical approval was requited in England and Wales (15/NE/0023) and Scotland (15/SS/047).

This is a request for some substantive amendments to be made to the IONA-Scotland protocol in the light of initial experience gained. Some non-substantial amendments are also notified. Note that unless stated as specific to the Scottish protocol, similar changes have also been subject to a protocol amendment application for England and Wales.

SUBSTANTIAL AMENDMENTS REQUESTED

1. Participant and exposure details

We have been asked by the Home Office to seek more detailed information about drug exposures in cases of severe toxicity, including data on the source of recreational drugs involved. We would therefore like to ask participants where they obtained these, with options being internet, shop, dealer, friend, relative or other. Participants can decline to provide this information if they prefer. Note that details of individual suppliers would not be sought. To allow this the structured data collection form has been amended and a copy is attached. Reference to this additional data has been added to the protocol (V2, 25th April 2016, p36) and the collection of this information is also now explained in the revised participant information sheet and consent form document (V2, 25th April 2016), which now includes the following in ‘What will happen to me if I take part?’

*‘The researcher will also record information about you including your age, sex and details about your recent drug use. They will also ask you what drugs(s) or substances you think you may have taken, when this happened and where the substances came from.’*

The following is also included in ‘What do I have to do?’

*‘Other than answering questions about recent drug use and providing the blood and urine specimens, you do not have to do anything. Note that you can decline to answer any questions if you prefer.’*Similar changes have been made to the Participant Information Sheet and Consent Form (Nearest Relative/Guardian or Welfare Attorney) document (V2, 25th April 2016).

1. Sample transfer arrangements

Most hospitals are asking for batching of samples to reduce administrative and transport costs. This means that there are further delays until the results of sample analysis are known. This is now explained in the information sheets as follows:

*‘Samples may be sent to the research laboratories in Newcastle or Edinburgh in batches every few weeks and this means that it will take longer for results to be available.*

1. Consent process

The original ethical application specified that consent would be taken by an ‘appropriately trained doctor in hospital’ (Section A18). However, it is difficult for some of the research sites to arrange that and we would like to modify the arrangement so that consent may be obtained by any appropriately trained staff member, with the decision on appropriate training made by the employing NHS Trust and with this delegation of responsibility recorded in the local delegation log.

1. Telephone consent

There have been isolated instances where samples have been secured in advance of consent when potential participants were lacking capacity, but the potential participant left hospital before formal consent could be obtained. In at least one case inclusion had been authorised by a designated consultee, but the participant has left hospital before it was possible to ask them to sign the ‘Consent form for persons previously included when they did not have capacity’. It should be noted that people can recover quite quickly from severe toxic effects and it is common for them to be discharged or take their own discharge at very short notice and often outside normal working hours.

We would therefore like to have mechanisms in place for obtaining consent from people who have left hospital but who were previously included on the basis of advice from a consultee when they did not have capacity. The process we are seeking authorisation for is that

(a) The patient is contacted by telephone to explain why they were entered in the study and asked if they would consent to the research team sending them an information sheet and the relevant consent form (These would be sent by post or email depending on expressed preference. A stamped addressed/freepost envelope will be included for postal returns of signed forms if this is the person’s preference. Note however that we anticipate that it will be unusual for postal returns of consent forms to be used by participants.

(b) A further telephone call is made to the participant a few days after the forms have been sent by the local researcher. (allowing at least 4 days for consideration and return of posted forms). For those willing to discuss consent by telephone, options given in the Consent form for persons previously included when they did not have capacity (1- remain in the study’, 2 - consent to data/samples collected so far to be used for research’ and 3 - do not consent to data/samples collected so far to be used for research) would be explained to the potential participant and their views recorded on the form by the person taking consent. This method of telephone consent has been used in other emergency department-based studies (e.g. Protocolised Management In Sepsis -ProMISe). The person taking consent would sign a declaration added to this consent form as follows:

*I certify that the participant has been sent a copy of the information sheet. I have explained the options available and answered all questions asked. I have recorded accurately on this form the wishes of this participant as discussed with me by telephone.*

1. Measurement of biomarkers for muscle toxicity

There is evidence that some NPS can cause muscle toxicity. Researchers in Edinburgh wish to use aliquots of blood/plasma samples provided to the study to measure potential miRNA biomarkers for muscle toxicity and correlate these with clinical data provided to the study such as creatine kinase, temperature etc. We have included background (P14-15) and methods (P40) for this in the updated protocol and an explanation of this in the participant information sheet as follows (in ‘What will happen with any samples?’)

*‘Research is also being performed at the University of Edinburgh measuring substances in the blood (‘microRNA’) that may be early indicators of adverse effects of drugs on muscle. A small amount of your blood sample will be sent from Newcastle to Edinburgh for this purpose.

All samples will only be labelled with your unique study code rather than your personal details. This means that the research teams at Newcastle University, the University of Edinburgh and the Scottish Police Authority Forensic Science Laboratory will not be able to identify who you are.’*

1. Participant numbers in Scotland

Original estimates of participant numbers in Scotland were made on the basis of rates of presentation to the Royal Infirmary of Edinburgh during 2014-5. However, presentation rates have fallen following successful local actions to reduce the sales and use of NPS. There may also be a further reduction in presentation rates when the new Psychoactive Substances Act comes into law. It is therefore appropriate to revise downwards the estimated numbers of participants from Scotland from the original figure of 400 to 200 (severe or non-severe toxicity) over 4 years. While this will reduce the amount of data available, it will not compromise the ability of the study to meet its aims.
2. Transfer of drug/product samples in Scotland.

Discussions have taken place between the PI in Edinburgh, Prof Eddleston, and the Scottish Police about appropriate methods for transporting samples of drug product (NPS packets/powders etc) that may be provided by participants alongside blood and urine samples. These drug product samples are extremely useful as they are easier to analyse for content than biological samples and once NPS have been identified in the product it is easier to confirm or exclude its presence in the biological samples. The issue is that these samples may contain substances controlled under current legislation (which may not be known by the user or clinician) and will almost always contain psychoactive substances the supply of which will be illegal when the Psychoactive Substances Act comes into law. The police have advised that these product samples can be sent to the Scottish Police Authority Forensic Science Laboratories with the biological samples covered by a memorandum signed by the local PI and the SPA FSL. A copy of the memorandum is provided with this application.

*IONA-S Memorandum – NPS packets V1.0, 4th April 2016*

NON-SUBSTANTIAL AMENDMENTS

We would also like to notify the REC about the following amendments that we consider to be non-substantial.

1. Inclusion criteria

We have clarified in the inclusion criteria (Protocol P26) that the study involves people with ‘suspected novel psychoactive substance exposure’ (previously ‘suspected recreational drug exposure’) to be consistent with other parts of the protocol.

Also, following feedback from research sites, we wish to define severe toxicity as participants who have (i) severe behavioural disturbances, even if not prolonged, (ii) myocardial infarction and (iii) acidosis as evidenced by a venous bicarbonate < 20 mmol/L (as some patients do not have arterial blood gases performed). Also, as most Emergency Departments are not familiar with the Poisoning Severity Score, relevant features indicating ‘severe toxicity’ (PSS3) using this scale have been included separately in the main list (Protocol P27). We would also like to allow local principle investigators to include patients if they have other manifestations of toxicity that they can justify as severe, because it is hard to predict all possible severe toxic effects that could result from exposure to novel psychiatric substances. (Protocol P26 and 27).

In order to verify whether included participants meet these criteria, the data collection sheet now asks what severity criteria are present when including the participant. (Note that for the Scottish protocol (unlike in England & Wales), severe toxicity is not one of the inclusion criteria). Explanatory notes have also been provided to ensure more complete and consistent data collection. A copy is attached as follows (also in protocol as Appendix 2) and is the same form as currently used in England and Wales.

*IONA data collection sheet, V2, 6th Jan 2016*
2. Consistency between protocols in England and Wales and Scotland

There is a separate protocol for England and Wales where separate ethical approval has been required. The protocol for IONA-Scotland has been revised to ensure consistency in arrangements as far as possible. Changes that have been made are minor (other than those described above) are tracked into the protocol.
3. Other administrative protocol changes

Details of research partners have been updated (Protocol P2-4). The recruitment algorithm has been corrected to remove a minor error (Protocol P32). Participant numbers have been updated in the Schedule of Events (P36) and in the estimated sample sizes (Protocol P 41) to be consistent with the Scottish ethical approval (Figures for England and Wales are not affected).

ST

25th April 2016