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The Emerging Drugs Network of Australia - Victoria (EDNAV) Clinical Registry: a state-wide illicit substance surveillance and alert network

Short title: The Emerging Drugs Network of Australia - Victoria

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SLG conceived and devised the study design in conjunction with JF under a University of Melbourne pilot project (Rapid and Precise Information on Drugs – RAPID). SLG was responsible for establishment of the study at participating hospital sites and overarching ethics approval. JS, RA, JAR, JK, JM, HH, LH, SH, EB and SLG were involved in planning site-specific methodology, project governance and reciprocal hospital site-specific ethics approvals. The first draft of the manuscript was written by RS, JS and SLG. All authors contributed and approved of the final manuscript.

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The Emerging Drugs Network of Australia - Victoria (EDNAV) Clinical Registry: a state-wide illicit substance surveillance and alert network

Abstract

Objectives: With an increasingly dynamic global illicit drug market, including the emergence of novel psychoactive substances, many jurisdictions have moved to establish toxicosurveillance systems to enable timely detection of harmful substances in the community. This paper describes the methodology for the Emerging Drugs Network of Australia - Victoria (EDNAV) project, a clinical registry focused on the collection of high quality clinical and analytical data from emergency department (ED) presentations involving illicit drug intoxications. Drug intelligence collected from the project is utilised by local health authorities with the aim to identify patterns of drug use and emerging drugs of concern.

Methods: The project involves ten public hospital EDs in Victoria, Australia. Patients 16 years and over, presenting to a network ED with a suspected illicit drug-related toxicity and a requirement for venepuncture are eligible for inclusion in the study under a waiver of consent. Clinical and demographic parameters are documented by site-based clinicians and comprehensive toxicological analysis is conducted on patient blood samples via specialised forensic services. All data is then deidentified and complied in a project specific database.

Results: Cases are discussed in weekly multidisciplinary team meetings, with a view to identify potentially harmful substances circulating in the community. High-risk signals are escalated to key stakeholders to produce timely and proportionate public health alerts with a focus on harm minimisation.

Conclusions: The EDNAV study represents the first centralised system providing near real-time monitoring of community drug use in Victoria and is fundamental in facilitating evidence-based public health intervention.

Key words: novel psychoactive substances, early warning system, public health, toxicosurveillance, illicit drugs

Introduction

In response to the evolving challenge of illicit substance use in Australia, public health bodies and advisory committees have called for enhanced public health measures, including greater visibility related to community illicit drug use[1, 2]. Of increasing concern is the emergence of novel psychoactive substances (NPS), often structurally modified traditional illicit substances with poorly described pharmacological and toxicological profiles[3]. While unadulterated NPS can be purchased online, NPS are increasingly being detected as drug adulterants whereby, unbeknownst to the consumer, they are cut with or added in replacement of a traditional illicit substance. This includes the recent deaths of five young Victorian men following the ingestion of illicit drugs that unknowingly contained two potent NPS[4].

The SARS-CoV-2 (COVID-19) pandemic has added additional volatility to the Australian illicit drug market with border closures and travel restrictions disrupting distribution channels particularly for import-dependent illicit substances[5]. This was reflected in consumer surveys reporting fluctuations in perceived drug costs and supply following the implementation of nation-wide lockdowns forcing many to source alternative substances[6, 7]. This drug substitution was also postulated to be a contributing factor influencing the increase in overdose fatalities related to a range of NPS plus cocaine, methylenedioxymethamphetamine (MDMA), and gamma-hydroxybutyric acid (GHB) seen in 2020[8]. Although opioid related fatalities did not increase to the degree observed in North America[9], Australia remains poorly prepared to rapidly detect non-fatal overdoses resulting from emerging high-potency synthetic opioids (including fentanyl and analogues) within the community.

To address these ongoing concerns, several Victorian government agencies recommended the development of a state-wide illicit drug early-warning system (EWS)[4, 10], highlighting the importance of data-sharing between emergency physicians, forensic laboratories, researchers, and health services[1, 2, 10]. Current monitoring modalities utilised in Australia, such as surveys[6], wastewater monitoring[11] and coronial investigations[8], lack the specificity and/or responsiveness required for an effective EWS. Individuals presenting to hospital emergency departments (EDs) with illicit drug toxicity are an important subgroup of people who use drugs that, by the nature of their hospital presentation, provide an opportunity to describe and quantify illicit drug-related harm. However, the International Classification of Disease (ICD) coding system currently used in hospitals is known to underestimate the extent of illicit drug intoxication presentations and no specific coding is available for NPS[12, 13]. Moreover, standard toxicological screening conducted by hospital pathology services are commonly limited to qualitative identification of broad classes

of substances, with no capacity to continually update illicit drug reference libraries or obtain the drug standards required to accurately quantify novel substances.

The development of clinical registries has been demonstrated to positively drive patient care outcomes[14]. In the context of ED illicit substance intoxication presentations, a clinical registry collecting demographic, medical and toxicological data provides a unique opportunity to facilitate toxicosurveillance in the community. Currently there are several such projects operational in Australia including, the Emergency Department Admission Blood Psychoactive Testing (EDABPT) program in South Australia, the Western Australian Illicit Substance Evaluation (WISE) study[15, 16].

This paper describes the Emerging Drugs Network of Australia - Victoria (EDNAV) project, a clinical registry focused on collection of high quality clinical and analytical data of ED illicit drug intoxication presentations from a network of Victorian hospitals. This includes the provision of in-depth toxicological analysis of patient blood samples and clinician-driven documentation of presenting cases. Ultimately, the EDNAV project aims to provide timely drug intelligence to state health authorities, facilitating public health interventions and harm minimisation strategy implementation.

Methods

The EDNAV project is a multi-centre prospective observational study, collating clinical and analytical information regarding illicit drug-related ED presentations within a purpose-built electronic registry. The registry is designed to facilitate regular, timely data analysis and subsequent risk assessment to inform community toxicosurveillance measures in the state of Victoria, Australia.

The EDNAV project was created in conjunction with a University of Melbourne pilot project (Rapid and Precise Information on Drugs – RAPID), utilising data from wastewater analysis, syringe residue analysis and ED illicit drug presentations to provide health authorities with intelligence on community drug use. The University of Melbourne Human Research Ethics Committee (HREC) provided approval for RAPID to utilise EDNAV registry data.

Austin Health (Heidelberg, Victoria) is the project sponsor and sentinel site for the EDNAV Clinical Registry. Ethics approval was granted by the Austin Health HREC (HREC/66506/Austin-2020), with reciprocal approval granted at ten sponsor hospital sites including nine metropolitan public hospitals; Austin Hospital (Heidelberg), Casey Hospital (Berwick), Dandenong Hospital (Dandenong), Frankston Hospital, Monash Medical Centre (Clayton), Northern Hospital (Epping), Royal Melbourne Hospital (Parkville), St Vincent's Hospital (Fitzroy) and Western Hospital (Footscray), and

one regional public hospital; Bendigo Hospital. The selected public hospital catchment areas cover a diverse range of Local Government Areas across the state of Victoria (Figure 1). A waiver of consent was obtained for inclusion of de-identified patient and analytical data in a secure clinical registry under Section 2.3.10 of the National Statement on Ethical Conduct in Human Research 2007 (updated 2018)[17].

The EDNAV Clinical Registry is hosted within the Research Electronic Data Capture (REDCap) secure web-based software platform hosted at Austin Health. REDCap is designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources[18, 19]. In accordance with best-practice operating principles for Clinical Registries, operations at each sponsor site are managed by the EDNAV Clinical Management and Steering Committee and the EDNAV Data Management Committee.

Operations across all hospital study sites are overseen and coordinated by the EDNAV Monitoring Team (EDNAV MT). The EDNAV MT consists of the study Principal Investigator (clinical toxicologist and emergency physician), clinical toxicologists/emergency medicine physicians, forensic toxicologists, academic researchers, public health officials, and consumer representatives. Each respective hospital site has a dedicated site-specific EDNAV Operational Team (EDNAV OT), which is responsible for the day-to-day project function.

During planning and creation of the EDNAV project, consultation was undertaken with investigators leading the Emerging Drugs Network of Australia (EDNA) project to enable future alignment and sharing of EDNAV project data within a national EDNA framework[20].

Registry eligibility:

Initial eligibility includes patients 16 years or older presenting to a network ED with a reported or suspected illicit substance exposure, associated with clinical signs of toxicity (Figure 2), and a requirement for venepuncture or intravenous cannula insertion as part of standard care. Patients are excluded if there are no clinical signs of illicit drug toxicity, no requirement for intravenous access or laboratory analysis of a blood sample, or where intoxication is believed to be solely ethanol related.

Case selection:

Quota sampling is currently employed as project funding limitations allows for analysis of up to 16 cases per week. Therefore, cases that initially fulfil study selection criteria are subsequently reviewed by EDNAV MT clinicians who apply purposeful sampling to select cases based on maximal benefit to potential drug intelligence. Priority is given for cases with severe toxicity requiring critical care bed admission and/or unexplained or unexpected symptoms. Cases requiring naloxone administration also are prioritised because of the desire to detect emerging opioids, which is likely to provide the greatest illicit drug-related threat to public health[21]. Once a case is selected for project inclusion, it is assigned an EDNAV Unique Registry Number (URN), which is subsequently used for all EDNAV registry related identification and correspondence.

Sample acquisition:

At the time clinically indicated venepuncture is undertaken, at least 1mL of blood is placed in a separate ethylenediaminetetraacetic acid (EDTA) tube. The sample is labelled with the patient's hospital identification sticker and stored in a dedicated project refrigerator (at 4˚C). After secondary case selection (described above), samples are relabelled with the assigned EDNAV URN. Patient identifiers are only visible to site investigating clinicians. Samples from cases not selected for further analysis are discarded in accordance with site-specific biological waste disposal procedures. Blood samples from included cases are couriered weekly to the Victorian Institute of Forensic Medicine (VIFM) for toxicological analysis.

Data registry – collection and management:

Clinical data (including demographics, physiological observations, and medical complications) for each case is entered directly into the EDNAV dedicated REDCap database by the site specific EDNAV OT, with each case only identifiable by the EDNAV URN. The EDNAV URN is linked to the hospital identification number in a secure spreadsheet, accessible only to the relevant EDNAV OT for the purpose of EDNAV Registry case completion within seven days post-discharge. After this time the hospital identification number is unlinked from the EDNAV URN, and the patient is no longer re-identifiable. The EDNAV Registry and the toxicological analysis results only reference the de-identified EDNAV URN to allow continuity of data entry and ensure confidentiality.

Toxicological analysis:

Patient blood samples collected are transferred via appropriate cold-chain requirements to the VIFM Toxicology Department on a weekly basis. Batch analysis is then undertaken, and toxicology results are reported to the EDNAV MT within 48 hours. Blood samples are analysed overnight via a liquid chromatography-tandem mass spectrometry (LC-MS/MS) screen targeting 327 common basic and neutral pharmaceuticals and illicit substances (including 77 NPS)[22], as well as a secondary NPS specific LC-MS/MS screen targeting 268 NPS including new opioids, benzodiazepines, stimulants, hallucinogens and synthetic cannabinoids (appendix 1). The NPS specific screen is actively updated based on emerging drug intelligence and literature reports.

Results

The primary objective of the EDNAV project is the development of a state-wide clinical registry containing data from illicit substance intoxication-related ED presentations to better characterise community illicit drug use. The EDNAV Registry functions within an integrated framework (Figure 3), with the main function to assess potential high-risk signals which can subsequently inform the implementation of specific and actionable public health interventions. The temporality between a patient's ED presentation and toxicological analysis, enables the EDNAV Registry to generate near real-time drug intelligence, thus hastening the response time to identified drug-related harms in the community.

Complex toxicological analysis of EDNAV samples is fundamental to the rapidity and precision of the drug intelligence generated by the EDNAV project. Importantly, the VIFM is well placed to provide comprehensive analytical drug screening, regularly updating its list of targeted substances from drug intelligence derived from casework and forensic laboratories in other jurisdictions. This ensures the EDNAV Registry continually provides relevant data even in the setting of drug market fluctuations, hazardous drug adulterations, and transient NPS detections, which would otherwise not be identifiable as part of routine clinical care.

The EDNAV MT meets formally every week to discuss cases from the preceding week, with allowance for ad-hoc meetings where high-risk signals emerge. Cases are evaluated in the context of previous EDNAV cases and drug intelligence from other toxicosurveillance sources to provide a robust assessment of potential community threats. Multilateral channels of communication established between the EDNAV MT, study sites and key stakeholders are

used to escalate high-risk signals to produce timely and proportionate public health intervention with a focus on harm minimisation. Thus far three public Drug Alerts have been issued from EDNAV cases, all related to the identification of NPS adulterants in traditional illicit substances[23].

Discussion

The EDNAV Registry represents the first state-based centralised system for reporting non-fatal illicit drug related intoxications managed in EDs within Victoria, with a focus on the identification of geospatial changes in drug use and emerging drugs of concern. The project was created to meet a need for real-time monitoring of acute harm resulting from illicit drug use, particularly in the setting of COVID-19 and associated illicit drug market volatilities. In-line with international EWS implementation guidelines, the EDNAV registry prioritises collection of high-quality clinical and analytical data to facilitate public health action based on scientifically rigorous drug intelligence[24].

Similar toxicovigilance programs have been successfully implemented both domestically and internationally, providing real-time data on community drug use. Elsewhere in Australia there are two other notable state-based illicit drug surveillance programs, EDABPT program in South Australia and WISE study[15, 16]. Of these programs, EDNAV derives data from the largest number of healthcare networks, with the total number of ED presentations across EDNAV network sites greater than 700,00 annually, representing ~40% of total annual Victorian public hospital ED presentations[25]. Although limited by the number of cases analysed per week, the diversity of EDNAV network sites is anticipated to enhance the quality and scope of drug intelligence.

Comprehensive toxicological analysis represents one of the most informative and reliable sources of data regarding community illicit substance use[26]. All three Australian studies employ a centralised system of toxicological analysis for patient blood samples utilising state-based forensic institutes[15, 16]. This enhances scientific rigour, providing high inter-sample validity, but also allows for detection of drug adulterants and novel drugs which would otherwise not be identified. Other programs prioritise capturing a breadth of cases over case-specific clinical data[16]. This contrasts with EDNAV, where the clinical registry captures detailed clinical data with a view to better understand the toxicological effects of NPS.

Establishing inter-institutional collaborations is of critical importance to the function of an EWS in facilitating informed drug risk assessments and appropriate dissemination of information[24]. The EDNAV MT and EDNAV OT represent a unique multidisciplinary network, bringing expertise from medicine, forensic sciences, and public health to enable a

holistic interpretation of drug intelligence. Specific signalling to alcohol and drug peer networks, community advocates and/or the public is facilitated by EDNAV MT public health representatives. The South Australian Drug Early Warning System (SADEWS), which utilises data from EDABPT, represents a more formalised state illicit drug EWS, but with similar established channels for communication with escalation through the South Australian Department of Health and Wellbeing[27]. The WISE study also alludes to an EWS function, with ability to escalate drug intelligence where necessary[15]. Eventually, data exchange between state-based projects and the national EDNA project will occur, facilitating a coordinated toxicosurveillance network spanning all Australian jurisdictions[20].

Limitations

Enrolment in the EDNAV Clinical Registry currently is based on purposive sampling methods, therefore resultant data may not be representative of the larger population of illicit drug users. As such, results will only be used to detect emerging NPS and analyse trends, not to provide prevalence estimates.

Substance identification is limited to the extent of validated substances in the VIFM LC-MS/MS screen. This may present an issue for NPS, where the substance itself and/or metabolites might be unknown or in low concentrations and therefore not detected as part of toxicological analysis. However, with regularly updated analytical methods incorporating new and emerging drugs based on local and international drug intelligence, it is likely most substances would be detected.

Conclusions

In the context of a dynamic global illicit drug market, many jurisdictions have moved to establish an illicit drug EWS to enable timely detection of harmful substances within the community. The EDNAV Registry is the first state-based, centralised system for correlating clinical and analytical data from non-fatal illicit drug-related hospitalisations in Victoria. Resultant data is used to detect emerging trends in illicit drug use in Victoria, providing near real-time drug intelligence to support other community toxicosurveillance measures. Through the establishment of an inter-institutional network of clinicians, toxicologists, public health officials and community advocates, the EDNAV project will refine and inform the implementation of evidence-based public health intervention and harm minimisation strategies.

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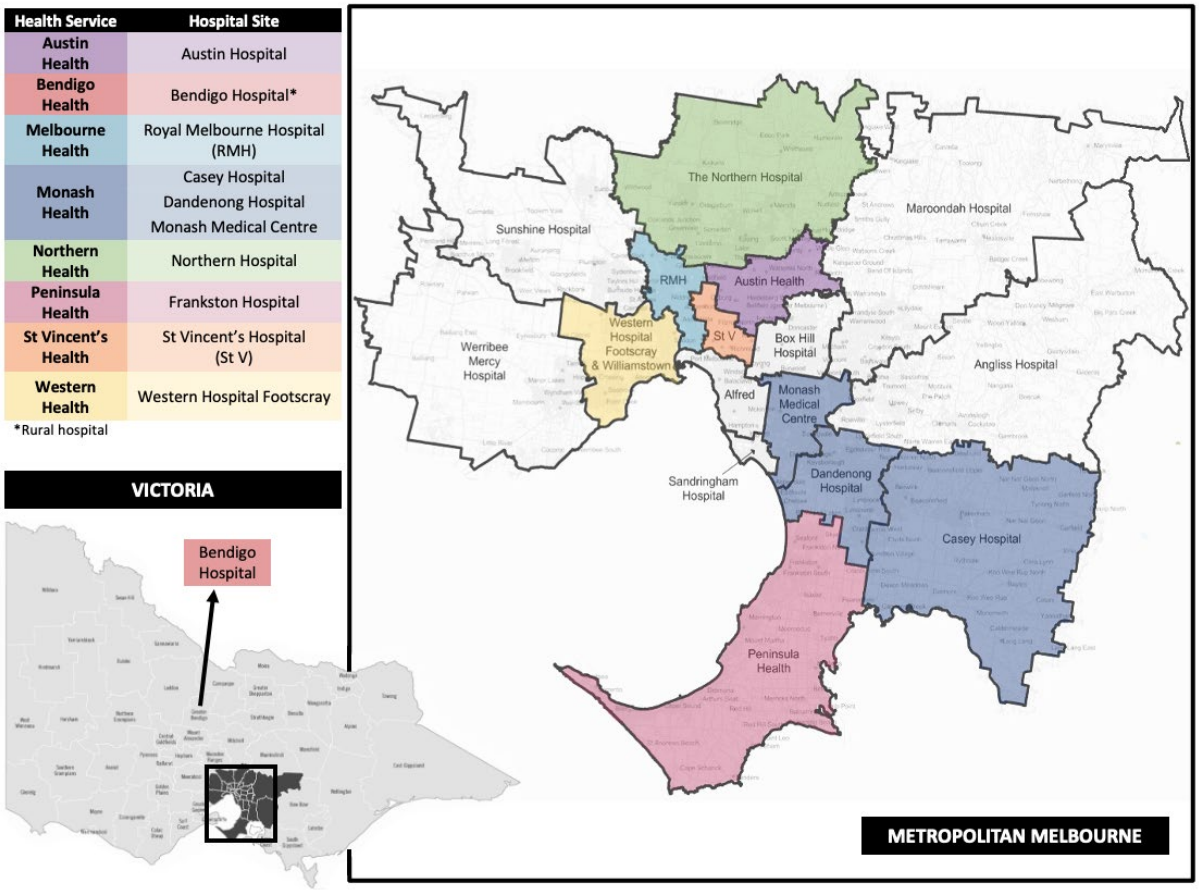

Figure 1. Map of Emerging Drugs Network of Australia - Victoria hospital study site catchment areas in metropolitan Melbourne, adapted with permission from Ambulance Victoria [28, 29]

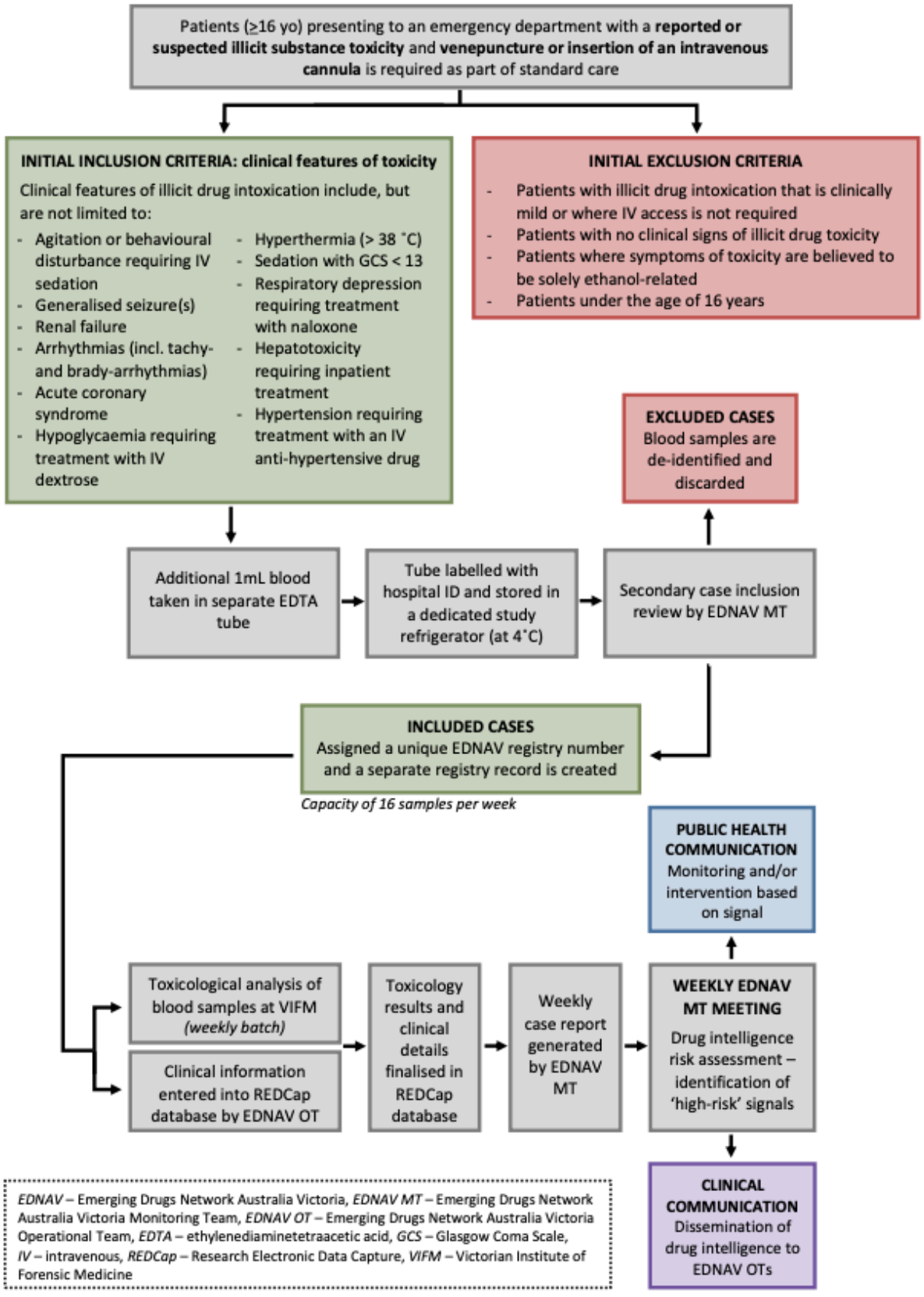

Figure 2. Emerging Drugs Network of Australia - Victoria Clinical Registry eligibility criteria and methodology flowchart

Note: please see attached pdf for higher resolution image of figure 2

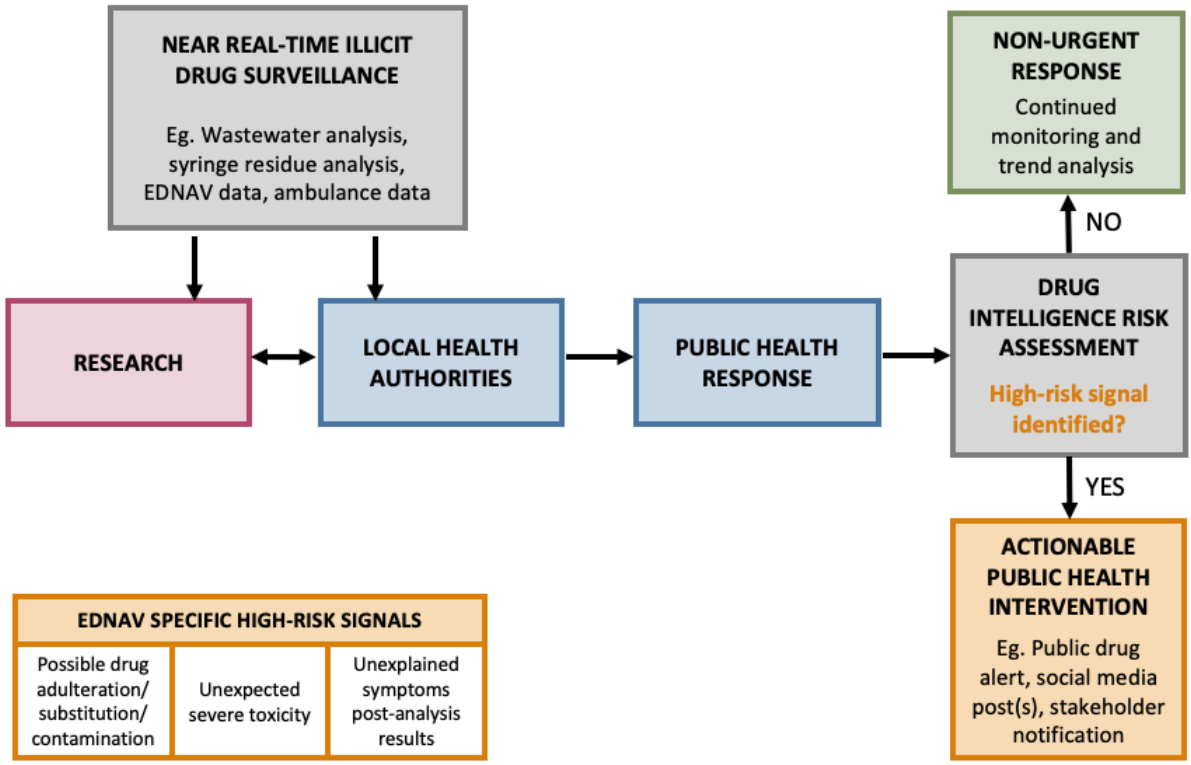

Figure 3. Framework for state-wide illicit drug toxicosurveillance, adapted from the World Health Organisation stepwise approach to surveillance of noncommunicable diseases [30]