EMERGING DRUGS NETWORK OF AUSTRALIA (EDNA)

Research Protocol

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1 Project Details			
Project Title:	Emerging Drugs Network of Australia (EDNA)		
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2 Rationale / Background

Use of illicit drugs is increasing, with many new synthetic drugs emerging at an unprecedented rate. In Europe, more than 100 new drugs were detected in 2014 alone.[1] The toxicity profiles of synthetic stimulants, hallucinogens, cannabinoids or opioids are often unknown, making effective clinical diagnosis and treatment difficult.[2] The recent Prime Ministerial National Ice Taskforce and the accompanying Council of Australian Governments National Ice Action Strategy highlighted trends in new and emerging drugs as a priority research area to better inform prevention and treatment responses.[3,4]

Multiple deaths in Australia have been attributed to Novel Psychoactive Substances (NPS), including a series of six deaths at festivals over the 2015–2016 summer season.[5] A fatality from 25I-NBOMe toxicity has been documented in Western Australia.[6] Clusters of patients have presented to the emergency department (ED) in a critical condition;[7] and recent cases of significant toxicity, including deaths in Queensland (October 2016), Victoria (January 2017) and Western Australia (February 2017), have been linked to NBOMe-type drugs.[8-10] Novel opioids including carfentanil have been detected in Australia, and carry increased risk of fatal opioid overdose in injecting drug users. The New South Wales Deputy State Coroner has just handed down findings related to five deaths at festivals related to illicit drug use in that state alone in the previous year.

International calls for further research into illicit drug use and NPS have suggested that improved collaboration between ED physicians, forensic laboratories, researchers and health services could help to identify new and emerging drugs more rapidly,[11] and provide more robust data on epidemiology and associated harms.[12] In Australia, information on trends in drug use is currently obtained through general or targeted surveys, police seizures, monitoring of internet fora, customs, pill testing, sewage monitoring, police roadside testing, coronial investigations and urine testing in police custody.[13–16] However, patients presenting to the ED are an important subgroup of drug users demonstrating harmful use by virtue of their presentation. Targeted research in this group will not only improve detection of more toxic substances, it is also likely to have a significant impact on the quality of care provided to patients presenting to the ED.

Until recently, treatment of patients presenting to ED with suspected illicit drug poisoning has been guided by symptomatology alone, with no knowledge of the agent responsible for toxicity. Standard care for prescription drug overdose can involve obtaining a blood sample to confirm diagnosis and inform appropriate treatment. This practice has developed from research, which has also identified the prescription drugs for which this is not helpful. The absence of similar objective standards for the assessment and management of illicit drug presentations is likely to explain the lack of confidence reported by clinicians in managing acute illicit drug toxicity compared to conventional drugs of abuse.[17]

The Western Australian Illicit Substance Evaluation (WISE) study commenced in 2016 at RPH and has provided high-quality information on drug use in patients presenting to ED. A unique approach to blood collection, storage, transportation and analysis across more than 600 patients enabled a range of NPS to be detected, including 25I-NBOMe and 25C-NBOMe (N-Bomb), PMMA (paramethoxymethamphetamine), 4-fluoroamphetamine, ethylone, methylone, diphenidine, synthetic cannabinoids FUB-AMB, AB-FUBINACA and cumyl pegaclone, and alpha-PVP (flakka). The sixteen 25C-NBOMe cases enrolled in the study thus far represent the world's largest case series of this drug. The study methods and laboratory analysis techniques have now been published,[18] and successful translation of the WISE methodology has enabled the introduction of Clinical Protocols for the assessment and management of illicit drug presentations at RPH as standard care. Importantly, these Protocols will now be introduced as standard care across multiple EDs in Western Australia and have been endorsed as best practice by the Australian National Poisons Network.

Drawing on the methodology and expertise gained from the WISE study, the investigators have partnered with Clinical Toxicologists and Emergency Physicians through the National Poisons Network with a vision of

forming the Emerging Drugs Network of Australia (EDNA). Never before has a coordinated national scheme enabling information sharing between clinicians and laboratories around the country been developed in this field. This collaborative network will work together to build a national clinical registry of illicit drugs resulting in ED presentations (EDNA Clinical Registry).

When designed and managed well, clinical registries provide a systematic and robust means of collecting, monitoring and analysing patient-level data to improve clinical care outcomes.[19,20] This is particularly important in an area such as illicit drug use given significant variations in diagnostic techniques, management and treatment outcomes. EDNA intends to utilise the expert collaborative networks already established to create a standardised, national surveillance system of illicit drugs of concern, using the technical infrastructure required of clinical registries. This aligns with key recommendations from the National Ice Taskforce, the National Centre for Clinical Research on Emerging Drugs and at a state level, the WA Methamphetamine Taskforce, for more sophisticated research on methamphetamine and emerging drug trends to improve data quality, inform alternative treatment approaches, and inform harm reduction strategies such as an early warning system.[3,21]

EDNA is seeking ethics approval under National Mutual Acceptance for the development of a de-identified national clinical registry on illicit drug use resulting in ED presentations. Establishment of a registry of this nature will take significant time and coordinated effort to ensure all ethical, legal and technical matters are sufficiently addressed. This Protocol outlines the way in which the collaborative team of investigators contributing to EDNA intend to navigate through important considerations including:

- Variations in legislative and governance requirements across institutions and jurisdictions;
- Data governance arrangements for state and national registries;
- Development of a standardised national minimum dataset;
- Uniform data collection methods across jurisdictions;
- System requirements to accommodate data from multiple state registries in a secure manner.

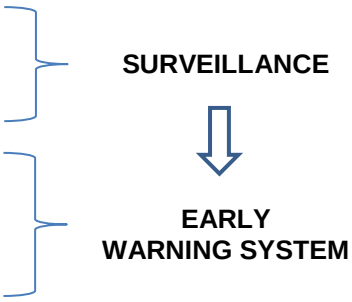
3 Project Aim and Objectives

3.1 Project Aim

The primary aims of the EDNA Clinical Registry are to:

(1) Improve the quality and safety of clinical care and patient outcomes by identifying particular substances causing harm, linking these to their clinical effects, and determining which treatment methods are most effective; and

(2) Develop capacity to act as an Early Warning System (EWS) to enable rapid identification and responses to public health emergencies such as harmful illicit drugs circulating in the community, particularly in the event of clusters of poisonings presenting to the ED



3.2 Registry Impact Objectives

The following objectives have been conceptualised into four key areas of impact to reflect our priority on measurable and translatable clinical research. Adapted from a published Research Impact Framework,[22] it is envisaged this will provide a structured approach to monitoring and evaluation.

1. **Research**: EDNA will develop the capacity for coordinated, timely and evidence-driven responses to reduce harms associated with illicit drug use.
2. **Service**: EDNA will improve clinical care through evidence-based treatment approaches and streamlined system processes to better manage, monitor and report illicit drug-related ED presentations.
3. **Societal**: EDNA will establish an EWS that enables information on illicit drugs of concern to be safely and effectively disseminated in real time to reduce harms in the community.

4. **Policy**: EDNA state and national collaborative networks will bring together cross-institutional expertise to inform policy governing clinical care, harm-reduction strategies and future research.

4 Governance

EDNA will establish three levels of strategic and operational governance to ensure all activities associated with Registry development and management are conducted within the ethical and scientific parameters stipulated within this Protocol.

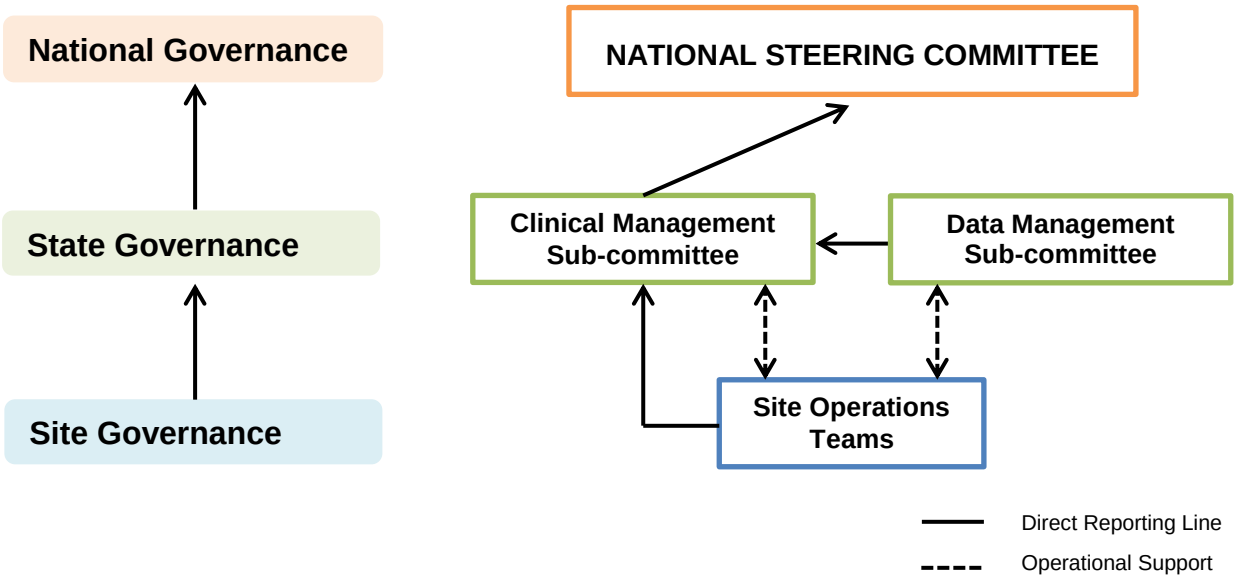


Figure 1. EDNA National Governance Structure

4.1 EDNA National Steering Committee

In keeping with best-practice operating principles for Clinical Registries established by the Australian Commission for Safety and Quality in Healthcare,[20] an EDNA National Steering Committee has been established and the first meeting scheduled for Q4, 2019. The National Steering Committee will provide expert oversight and strategic direction to ensure all activities across participating states maintain alignment with the development of a standardised and robust national registry.

4.1.1 Membership

The National Steering Committee will include:

- Senior Emergency Physicians from each sentinel hospital
- Clinical Toxicologists from each jurisdiction
- Project Sponsor (Centre for Clinical Research in Emergency Medicine, RPH)
- Lead Statistician
- REDCap Expertise
- Registry Host Representative - Curtin Health Research and Data Analytics Hub
- Consumer Representative
- Representative from National Centre for Clinical Research on Emerging Drugs (NCCRED)
- EDNA Registry Coordinator

It is acceptable for one member to fulfil the role of multiple representative positions. Members are also likely to sit across multiple governance levels (i.e. State and Site levels in the case of Principal Investigators).

4.1.2 Operations

Terms of Reference for the National Steering Committee will be collectively established and enacted. The following details will be included:

- Membership: proposed biannual review and expectations surrounding contribution
- Schedule of Meetings: quarterly meetings via video conference for interstate members
- Quorum requirements: proposed number and representation
- Declaration of conflict of interest
- Confidentiality Agreement

4.1.3 Responsibilities

The responsibilities of the National Steering Committee will be to:

- Provide expert oversight and strategic direction over all Registry activities, including that of the Sub-Committees.
- Establish policies and procedures that will underpin the Registry, including:
    - A standardised national minimum dataset;
    - Data Dictionary;
    - Data Access and Privacy Policy;
    - Publication and Release of Information Policy.
- Provide ongoing review of:
    - Data management processes, including the quality and efficiency of collection and reporting;
    - Registry performance in line with its objectives and effectiveness in meeting these;
    - All reports and information disseminated by the Sub-Committees;
    - All research and data requests relating to the Registry
- Advise on:
    - Communication strategies, including with consumer groups and the community;
    - The collection and interpretation of data
- Develop, approve and/or facilitate:
    - Major operational changes in response to matters put forward by the Sub-Committees, including any amendments to this Protocol if and when necessary;
    - Policies to maintain data governance, quality and security, particularly as contribution to the EDNA Registry expands;
    - Risk mitigation strategies to manage and/or resolve issues identified by the Sub-Committees (i.e. clinical quality and safety).

4.2 Clinical Management Sub-Committee

Each state jurisdiction contributing to the national Registry will establish a Clinical Management Sub-Committee (CMSC) to provide oversight of clinical implementation, data collection and reporting requirements at a local level. Each CMSC will be responsible for coordinating implementation of the standardised surveillance system across local sites, which will then feed into the national registry.

4.2.1 Membership

Each CMSC will comprise:

- Senior Emergency Physicians from participating local hospitals (Clinical Champions)
- Clinical Toxicologists from participating local hospitals
- Representation from central forensic laboratory
- Senior representation from the Data Management Sub-Committee
- Lead Researchers
- Local Consumer Representative

4.2.2 Operations

The CMSC will convene quarterly (to be scheduled the month prior to the National Steering Committee meeting) and have the provision for the calling of extra ordinary meetings as required. A Senior Physician from this Sub-Committee (ideally located at the sentinel hospital in each respective state and also a member of the National Steering Committee) will be required to attend and contribute to meetings of the Data Management Sub-Committee, or nominate a suitably qualified representative. The CMSC will report directly to the National Steering Committee.

4.2.3 Responsibilities

The CMSC will be established to advise on clinical matters arising from the Registry data, including quality of care and/or any serious events that become apparent.

The responsibilities of the CMSC will be to:

- Monitor implementation of standard care Protocols for the assessment and management of illicit drug-related ED presentations;
- In consultation with the Data Management Sub-Committee, provide oversight of Registry development, management and resourcing for the respective state jurisdiction;
- Ensure compliance with requirements of ethics committees and relevant legislation;
- Ensure data collection and data quality processes across hospital sites function effectively and in a timely manner;
- In the event of a cluster of illicit drug presentations, coordinate information sharing between key agencies and service providers (i.e. the network of participating hospitals, Ambulance services, collaborating forensic laboratory, Police, health and government authorities), rapid analysis of blood samples and agreed responses to reduce further harms in the community;
- Where clinical concerns require action, an escalation policy will be employed to drive quality improvement and this process will be overseen by the CMSC, with all major clinical issues and concerns reported to the National Steering Committee;
- Ensure finances of the Registry in their respective state are audited in accordance with appropriate standards and that audited statements are provided to the National Steering Committee;
- Communicate knowledge, output and lessons learned between investigators, clinicians, government and other relevant stakeholders;
- Provide reports and liaise as necessary with Registry funding bodies and ethics committees;
- Provide quarterly progress reports to the National Steering Committee.

4.3 Data Management Sub-Committee

A Data Management Sub-Committee (DMSC) will be established in each state jurisdiction to provide technical expertise and oversight of Registry development, security and maintenance. This Sub-Committee will work closely with their respective CMSC to meet the operational requirements of the Registry.

4.3.1 Membership

The DMSC will comprise:

- National Data Custodian
- Local Registry lead / host
- Senior representation from the Clinical Management Sub-Committee
- Clinical research representation from each hospital site
- Statistician

4.3.2 Operations

The DMSC will convene quarterly and have the provision for the calling of extra ordinary meetings as required. The local Registry lead / host will be required to attend and contribute to meetings of the CMSC, or nominate a suitably qualified representative.

The DMSC will report directly to their relevant CMSC and will provide direct support to Site Operation Teams when necessary.

4.3.3 Responsibilities

The role of the DMSC in each state jurisdiction will be to:

- Establish EDNA REDCap User Manual;
- Manage all technical aspects of the Registry infrastructure and functionality;
- Communicate with Registry leads in other jurisdictions to ensure consistent design and operational standards are met;
- Optimise levels of information and system security;
- Manage data monitoring and quality control processes, respond to identified risks and report any issues to the CMSC for escalation to the National Steering Committee if necessary);
- Monitor and report all requests for data access to the CMSC. Provide access rights only after permission has been granted by the National Steering Committee (via the CMSC);
- Facilitate statistical analysis;
- Facilitate the integration of independent state registries into the national EDNA Registry.

4.4 Site Operations Team

Site Operations Teams will be established in each participating hospital and will play an integral role in facilitating clinical implementation, data collection and timely reporting. Site Operations Teams will be led by 'Clinical Champions' (in most cases a Senior ED Physician) and will comprise a small number of physicians, clinical toxicologists and nurse researchers/research support staff who will oversee the day-to-day clinical operations, data collection, data entry and reporting.

Each Clinical Champion will be required to report on the progress and performance of their site, report any issues arising and attend meetings of their relevant state CMSC. Members from the DMSC will be expected to provide Registry support across Site Operations Teams in their state jurisdiction.

5 Registry Population

5.1 Eligibility Criteria

The EDNA registry will comprise de-identified information from patients who present to participating Emergency Departments and meet the below eligibility criteria:

5.1.1 Inclusion Criteria:

Clinical features of severe illicit drug intoxication include:

1. *Stimulant toxicity* (sympathomimetic or serotonergic or anticholinergic toxicity)
    1.1. Patients requiring intravenous sedation for manifestations of toxicity (i.e. not just psychologic manifestations related to methamphetamine-induced psychosis);
    1.2. Patients with illness critical enough to require ICU level care.

2. *Hallucinogenic toxicity*
    2.1. Patients requiring intravenous sedation for manifestations of toxicity;
    2.2. Patients with illness critical enough to require ICU level care.

3. *Opioid toxicity*
    3.1. Patients requiring a large initial dose of naloxone (e.g. >400microg in first hour);
    3.2. Patients requiring multiple repeat doses or an infusion of naloxone;
    3.3. Patients with illness critical enough to require ICU level care.

4. *Other*

In addition to the above clinical features of stimulant or opioid toxidromes, other suggestive features of illicit drug toxicity will be sought to determine eligibility, including reports of recreational drug use by the patient or others, presentation from a public event (e.g. festival or concert) and/or multiple patients from the same location presenting with similar clinical features.

5.1.2 Exclusion Criteria:

1. Patients with recreational drug intoxication that is clinically mild or where intravenous access is not required;
2. Patients presenting with agitation that is considered by the clinician to be predominantly related to methamphetamine-induced psychosis without significant physiologic manifestations suggestive of acute drug intoxication;
3. Patients under the age of 16 years.

5.2 Participation in the EDNA Registry

EDNA is seeking ethics approval for full waiver of consent to have the de-identified data of eligible patients included in the National Clinical Registry. Patient recruitment at a participating site will not commence until a Principal Investigator has been appointed to take responsibility for the data collected at that site, and site-specific governance approvals have been obtained. All patients who meet the above eligibility criteria and present to a hospital with site-specific governance approval will be eligible for inclusion in the EDNA National Registry.

In order to meet the operating requirements of clinical quality registries, investigators must ensure that complete data are collected from the entire eligible population.[19] The establishment of a de-identified national Registry with the capacity to translate evidence, improve the quality of clinical care and act as both a surveillance programme and an Early Warning System to reduce harms associated with illicit drug use meets key ethical (National Statement on Ethical Conduct in Human Research [The Statement], 2015)[23] and legal (NHMRC Guidelines approved under Section 95A of the Privacy Act 1988)[24] requirements for waiver of consent as follows:

- Relevant to the public health and public safety **benefits gained** from an evidence-based surveillance and Early Warning System, there is **minimal risk of harm** to an individual whose health information is collected, stored and used in a de-identified manner from pre-existing medical records collected as part of standard care;
- It will be **impracticable to obtain consent** from patients presenting to ED under the influence of illicit drugs for the following reasons:
    - Eligible patients are intoxicated and of altered mental state and thus are unable to provide valid consent at the time of enrolment. It is not ethical to approach the next of kin or companions of these patients, as this would violate the privacy of those who may not wish to divulge that they had potentially taken illicit drugs;
    - Difficulties around obtaining retrospective consent include the fact that patients may be fit for medical discharge with a companion or family member prior to being lucid enough to give informed consent. Also, many discharges occur overnight when research and clinical toxicology staff are not present. Contacting patients after discharge through telephone carries **a privacy risk** depending on their company at the time of the phone call. Similarly, electronic or written communications post discharge may inadvertently violate the patient's privacy if discovered. Finally, it is possible that death could occur as a result of the drug use, thus precluding consent;
    - It has been repeatedly demonstrated in quality improvement programs that requiring specific permission in advance from potential research participants (opt-in) will lead to the collection of a relatively small fraction of eligible cases and the resulting data will have no credibility for quality improvement;
    - Implementing a uniform opt-out approach is also not a viable option for this patient population given their often brief interaction in the emergency care environment and impaired capacity for verbal or written communication. Unstable living environments and limited resources to enable post-discharge communication provides further barriers for this group;
- The minimal risk of harm, protection of privacy and confidentiality, and benefits of contributing information to improve knowledge, quality of care and patient outcomes suggests there will be **no known or likely reasons for thinking that participants would not have consented** if they had been asked;
- As indicated above, the **protection of patient privacy at all times** will be highly dependent on the above requirements for consent being waived. This will be supported by strict policies governing de-identification processes, data storage and access permissions to protect patients from future legal ramifications related to their participation in the study;
- All data transferred, stored and made available for analysis and reporting from the EDNA Registry will be de-identified and protected by secure access controls as described in Sections 7 and 8 of this Protocol to ensure the **confidentiality of data is maintained**;
- Knowledge gained from the EDNA Registry will likely be of significant importance for the **health and well-being of patients**. Collaboration and information sharing with community and consumer representatives (i.e. Peer Based Harm Reduction WA) will provide important opportunities to make information arising from EDNA available to consumers;
- The nature of this project and de-identified information to be collected and reported on carries no potential for the **commercial exploitation** of derivatives of the data or deprivation of financial benefits to which the patients would be entitled;
- The EDNA Registry is seeking waiver of consent under National Mutual Acceptance. However, where a participating site lies in a jurisdiction where **waiver of consent is prohibited by State law**, an alternative method of consent will be sought.

6 National Registry Infrastructure

Development and full functionality of a standardised national registry and EWS will take significant time. This will predominantly relate to the need for site-specific governance approval across all participating public hospitals and ethics approval at private sites. During this period, work will commence on designing and building the technical standards required for successful configuration and deployment of a national registry. This process will be governed by the National Steering Committee and technical expertise provided by the Data Management Sub-Committees located in each state. The following describes the two key stages of development for the EDNA Registry under national arrangements. Figure 2 displays the flow of information from a hospital site level (initial WA hospitals identified for participation), to the Federation of State Registries, and their eventual contribution to the National Registry.

6.1 Federation of State Registries

The initial three years of the project (2020 – 2022) will prioritise development of individual state registries using a standardised dataset and an online, secure platform for the collection and storage of data (REDCap). Standardisation of these elements has already commenced through the National Steering Committee (i.e. development of a national minimum dataset and use of REDCap as the data storage and management platform) and will be essential to mitigate variances in governance landscapes, technology and infrastructure across states and territories. Using this co-location approach, each jurisdiction will be responsible for providing infrastructure, management and operational resources.

During this period, work will be undertaken by the Health Research and Data Analytics Hub at Curtin University to create the more sophisticated national infrastructure for migration of independent registries into a centralised system.

6.2 National Infrastructure Model

The ultimate vision for EDNA is a standardised national surveillance system that assembles the federation of state registries into a secure central platform. This national surveillance system will have the capacity to identify the illicit drugs causing greatest harm, analyse trends in use and clinical effects, and report on outcomes of interest. It will also inform the development of the National Prompt Response Network, which is a unique data sharing platform being developed by NCCRED to provide a comprehensive, evidence-base of illicit drug use and associated community level impacts. This system intends to draw information from Police, Coronial data, user groups and the general public.

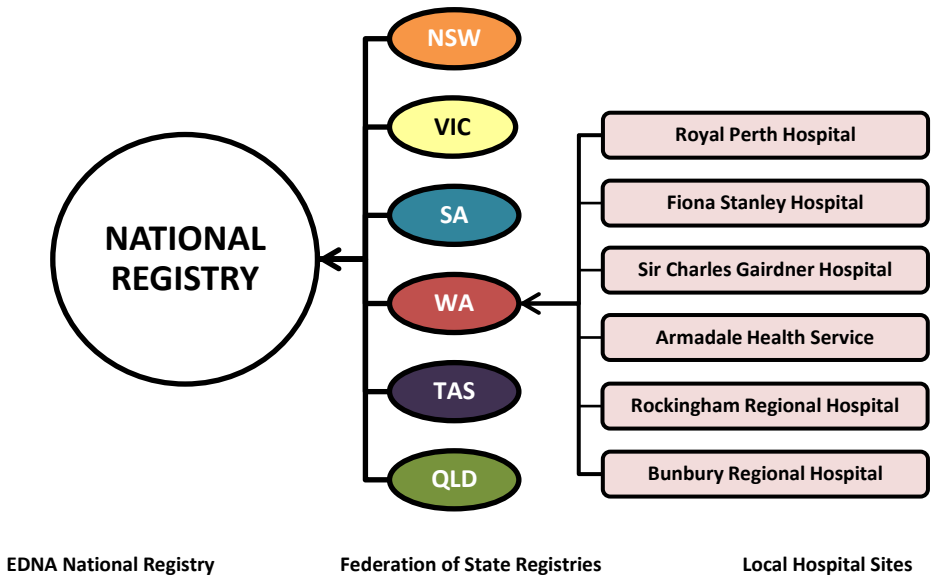


Figure 2. Stages of Development of the EDNA National Registry

7 Data Collection and Storage

7.1 Dataset

EDNA will collect a nationally endorsed standard minimum dataset of illicit drug use resulting in ED presentations. Data elements will be restricted to those considered essential and that comply with standardised medical terminology and data definitions. Where possible, elements and metadata specifications will align with data items specified in the National Health Data Dictionary (NHDD). However, given expectations of collecting unique information on new and emerging illicit drugs of concern, dataset specifications endorsed by the National Steering Committee will be applied to ensure uniform data collection is achieved.

The National Steering Committee will be responsible for overseeing the development of the Registry Data Dictionary. This task will coincide with development of the standardised national dataset and will provide a catalogue of all data elements contained in the Registry, including:

- Description;
- Variable source;
- Coding information;
- Normal ranges for elements when known.

Development of a standardised data dictionary will ensure data is consistent and uniform, providing reliable and comparable data for analysis. Sufficient clinical information on eligible patients will be required to reduce the potential for selection bias and to ensure accurate determination of outcome variables (i.e. treatment efficacy and patient outcomes). This will include collection of relevant pre-hospital information (i.e. ambulance / paramedic reports), initial symptomatology on presentation and patient records up until the time clinical outcomes can be reasonably ascertained. Independent approvals will be sought by jurisdictions wishing to collect data outside the scope of the agreed minimum dataset for the EDNA Registry.

7.2 Data Collection

Data collection procedures implemented as part of this project will not impact on the provision of health care or confidentiality of patients presenting to ED. These requirements are already in place at RPH as part of standard care protocols for the assessment and management of illicit drug ED presentations and will be expanded to other hospitals in WA shortly. As mentioned previously, these protocols have also been endorsed nationally as best-practice by the National Poisons Network, and have been shared with representatives on the National Steering Committee for approval across their local hospital network.

Data collection on eligible patients will occur at each participating hospital and will be overseen by the appointed Clinical Champion for that site. CRFs will be completed by trained ED staff (i.e. physicians, toxicologists, clinical nurses) and will be completed as close as possible to the time and place of care. Paper and electronic versions of the CRF will be available for initial data capture, and data entry delegates will ensure information from all CRFs is entered into REDCap and cross-checked for accuracy. During this process, patients will be assigned a unique REDCap identifier to protect the confidentiality of their records. However, it is important to note that information on file prior to assignment of a unique identifier will comprise information routinely collected for the patient's medical record.

One CRF will be completed for every relevant ED presentation. Therefore, any subsequent readmissions will be captured on additional CRFs and entered as new presentations.

De-identified toxicology results linked to the patient's REDCap identification number will be obtained from the relevant forensic laboratory (i.e. WA ChemCentre) for inclusion in the patient's central record. As detailed in the CRF, this will include information on substance/s detected and their concentration/s to enable matching with clinical effects and treatment outcomes recorded at the hospital site.

7.3 Data Transfer

Transfer of data into the central Registry database will occur in two stages:

- *Hospital site to state registry*: each hospital site will enter the required minimum data into REDCap to enable web-based submission to the relevant state registry for storage, cleaning and quality checking.
- *State registry to National Registry*: each state registry will utilise secure web-based mechanisms to transfer data into the central EDNA Registry.

Following sufficient testing of security controls (i.e. secure access, electronic transfer and electronic messaging systems) and data quality (i.e. reliability, validity and completeness), the goal is to create a National Clinical Registry with the technical capabilities to automate data transfer processes securely and efficiently from each state registry.

7.4 Data Storage and Security

Appropriate data storage and security controls will be established and maintained in accordance with ethical protocols and relevant legislation. Signed agreements for the storage of data will also be established within each participating health service.

The National Registry will be housed on a secure server at Curtin University. Curtin University databases are housed and managed in an ISO 27001 certified environment. The ISO 27001 certification incorporates the Privacy Act (1988) and Health Records Act (2001) within its Applicability Statement.

The EDNA Registry will be stored on a partitioned section of the server so it can only be accessed by authorised Project Investigators, Curtin Health Research and Data Analytics Hub staff and authorised IT personnel. Applications housed within the data centres are backed up nightly. Curtin University database security is maintained using:

- Encryption of data;
- A managed and audited protocol for access;
- Training and accreditation of personnel;
- Role-based access; and
- Authentication of data.

Paper records will be managed and stored according to in-hospital data retention and storage policies.

All decisions made by the National Steering Committee relating to data storage and security will align with the principles of responsible and accountable research practice set out by the Australian Code for the Responsible Conduct of Research (The Code),[25] including data and record management.

8 Data Management

A key role of the National Steering Committee will be to establish data management policies and procedures for the development of a clinical registry under national arrangements. Matters relating to custodianship, access and data release / publications will be made explicit in Contract and Funding Agreements between the various parties associated with the Registry prior to the commencement of the project. These Agreements will explicitly outline obligations regarding confidentiality and security of data to ensure efficient, effective and appropriate use of information and to mitigate risks associated with information sharing.

8.1 Data Ownership

In line with best practice data management principles outlined in The Code[25] and its supporting documentation,[26] Agreements covering ownership, stewardship and control of data will be in place across jurisdictions participating in the Federation of State Registries. A national Data Ownership Agreement applicable to the EDNA Clinical Registry will be in place between relevant parties before data transfer from State Registries.

For the Western Australian State Registry, the Project Sponsor (Centre for Clinical Research in Emergency Medicine) will have custodianship of the data, which includes accountability for the privacy, security and integrity of patient information held within the registry. In accordance with confidentiality requirements, legislation, privacy rules and other guidelines, all permissions for data access must be approved by the Sponsor and the National Steering Committee as the governing body.

All hospital data (i.e. held within hospital information systems) remains the property of that institution. Curtin University (via the Curtin Health Research and Data Analytics Hub) will be the administering institution for the collective Registry data and data management systems, and will manage funds provided to establish and maintain the EDNA Registry.

8.2 Data Access

Access to the national REDCap database will be controlled by the Project Sponsor and Coordinating Chief Investigator. All Principal and Associate Investigators (and members of the Research Group when deemed appropriate) will be required to complete a registration form prior to gaining access to the Registry. A unique access code will be provided to each user to control access and track online usage.

The new knowledge on illicit drugs and evidence of best practice in Emergency care that is likely to come from the EDNA Registry is likely to generate significant interest from researchers and institutions, both nationally and internationally. All external requests for data access must be granted by the National Steering Committee and will require Institutional Ethics Committee approval. While the personal health information of Registry participants will be protected through the de-identification of their records prior to migration into the national Registry, requests to access the data and subsequent use of the data will be closely monitored by the National Steering Committee. The National Steering Committee will also restrict the distribution of data that identifies participating institutions until data quality has been validated and appropriate legal protection obtained.

The host Institution (Curtin University) will be granted access to the data via qualified IT personnel to enable quality checks and system-level management. This will be governed by confidentiality requirements, legislation, privacy rules and other guidelines.

8.3 Data Retention

It is intended that EDNA will be an ongoing national Registry. If EDNA ceases to operate, data will be held by the host institution (Curtin University) in accordance with the Australian Code for the Responsible Conduct of Research. Contractual agreements will accommodate regulatory and sponsor (RPH) requirements for the minimum retention period of hospital records. Registry data cannot be reassigned or transferred without written approval from the Project Sponsor and National Steering Committee.

9 Data Quality Control

A quality assurance plan will be collectively developed by members of the Data Management Sub-Committees for endorsement by the National Steering Committee. This procedural document will detail the key requirements to be carried out at each level of implementation (hospital sites, state registries and national registry) to ensure outcomes reported are derived from valid and reliable data sources. Three processes will be undertaken to produce high quality data for the national registry.

9.1 Data Cleaning

Routine data cleaning will be required at each hospital site prior to uploading the data to the relevant REDCap registry. This process is intended to identify incomplete, inaccurate or corrupt records and then correcting or deleting them. Ideally, a designated person from each hospital site will be responsible for cleaning the data. Where this is not possible, data cleaning will be undertaken by the EDNA Coordinator for the relevant state. Any anomalies or data quality issues identified at this point will be raised with the Principal Investigator for the relevant site in the first instance, and escalated to the Data Management Sub-Committee when necessary. Data cleaning will ensure that data for all relevant cases is being captured in a timely and accurate manner.

9.2 Data Monitoring

Data monitoring will fall under the jurisdiction of the Data Management Sub-Committees and will provide a structured approach to review the standard of data collected and recorded in accordance with ethical and regulatory standards and protocols endorsed by the National Steering Committee. EDNA Master files will be located in all hospital sites and will contain detailed documentation and templates relating to the project (e.g. Ethics Protocol, site specific approvals and amendments, policies and procedures governing all aspects of conduct, data collection templates and data dictionary, REDCap user instructions, site and investigator contact details etc.). Data monitoring activities will be closely aligned with the endorsed minimum dataset.

9.3 Data Auditing

A formal auditing schedule will be implemented upon commencement of each state registry to ensure the data uploaded to the national registry has been sufficiently validated. This will entail quality checks against key outcome indicators endorsed by the National Steering Committee in a random sample (estimated 10 percent) of cases. This suite of indicators will serve as reference points for national monitoring and auditing to ensure the registry is capturing what it intends to (i.e. validity) and that it is being uniformly collected across sites (i.e. reliability). The following areas of interest are likely to guide the development of indicators:

- Identification of illicit drugs causing harm and blood concentration/s;
- Associated clinical effects (observed/reported, vital signs, ECG, other clinical findings);
- Medical intervention / treatment provided;
- Patient outcomes;
- Length of stay in hospital;
- Referrals to specialist care / services;
- Injuries to patient / staff;

To ensure consistency across jurisdictions, all audits will be conducted by nominated members of the Data Management Sub-Committees with expertise in the management of clinical registries and/or relevant experience in data auditing processes. It is estimated that State registries will be audited bi-annually once deemed operational. The national registry will be subjected to formal auditing on an annual basis and results reported to the National Steering Committee. It is anticipated that this frequency will be sufficient enough for issues with data quality (i.e. incomplete and/or inaccurate) to be identified quickly and resolved.

10 Data Analysis and Impact Outcomes

10.1 Statistical Plan

As part of the auditing process, de-identified summary reports will be compiled for internal distribution to participating sites. These will be produced bi-annually and will contain descriptive level statistics relating to

participation and quality indicators as discussed above. At a national level, reports will be generated annually following the commencement of the registry. Permissions will also be granted for investigators to conduct ad-hoc analyses of data contributed from their site to enable additional monitoring. Expert statistical and epidemiological advice will be sought to maintain the scientific rigour of data analysis and interpretation of findings.

Characteristics of the study population and for the subgroups testing positive to individual drugs will be tabulated using counts and proportions, means and standard deviation or medians and interquartile ranges as appropriate. Dichotomous variables such as the presence of clinical signs (physiological and/or psychological) will be compared between drug groups using chi-square test or Fisher's exact test. Continuous variables such as psychological, physiological and laboratory parameters will be analysed using linear regression where assumptions are met or following log transformation for non-normally distributed outcomes. Where transformation fails to achieve normality and homoscedasticity, non-parametric tests such as the Mann-Whitney U test and Kruskal-Wallis test will be used.

10.2 Impact Analysis

The significant time required to establish a national clinical registry means the conduct of meaningful outcome evaluation will be unrealistic and likely detrimental to the quality of findings if reported prematurely. An Evaluation Plan will be developed for endorsement by the National Steering Committee and will contain an Outcomes Measurement Framework detailing short, medium and long term outcomes and the methods by which these will be evaluated.

Progress towards project aims and impact objectives listed in Section 3 will be reported at a jurisdictional level by Q4, 2022. This will ascertain preliminary trends in the data, allow initial comparisons between states to be conducted and identify areas for quality improvement prior to national registry evaluation in Q4, 2024.

11 Reporting and Dissemination

A strict timeline of reporting will be maintained in accordance with ethics, governance and funding body requirements. Once operational and quality assurance measures have taken place, key outputs from the EDNA registry will be disseminated to professional and clinical audiences via peer-reviewed publications, conference presentations, institutional reports and other credible communication channels.

We anticipate the process of development and the outputs generated from the EDNA registry will attract significant international interest. The National Steering Committee will be responsible for approving all information requests and communication strategies that relate to the national registry. Acknowledgment protocols will be developed to ensure contributing institutions, investigators, funding bodies, ethics committees and the Project Sponsor are cited. Hospitals will have authority to access, use and report on site-specific data stored in the online database.

The timing and methods of public release of information will be carefully managed by the National Steering Committee to ensure the nature of information released and intended audience are controlled. Collaborations with community-based organisations, consumer representatives and public health and government agencies will provide critical mechanisms to distribute targeted and safe harm reduction messaging.

Finally, we envisage ongoing opportunities for information sharing and clinical translation using the collaborative networks established for EDNA. This will include dissemination of effective, evidence-based clinical protocols and treatment options to improve outcomes associated with illicit drug-related ED presentations.

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