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SPECIAL ARTICLE

From Patient Registry to Multi-Center Research Consortium: the Toxicology Investigators Consortium (ToxIC) Turns Fifteen

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Abstract

The Toxicology Investigators Consortium (ToxIC) was launched as a prospective multi-center registry of cases who receive medical toxicology consultations. Now, with over 100,000 cases, the Core Registry continues to address many medical toxicology research questions and has served as the foundation for multiple sub-registries, including the North American Snakebite Registry and the Medications for Opioid Use Disorder sub-registry. ToxIC also has evolved a portfolio of non-registry-based projects utilizing medical toxicology physician site principal investigators who enroll patients through emergency departments, irrespective of whether they received a medical toxicology consultation. These studies include the FDA-ACMT COVID-19 ToxIC Pharmacovigilance Project, which identifies adverse drug reactions related to the treatment of COVID-19, the Fentalog Study a toxico-surveillance study of suspected opioid overdose cases, the Drug Overdose Toxico-Surveillance Reporting Program which enrolls either suspected stimulant or opioid overdose cases, and the just being launched Real-World Examination of Naloxone for Drug Overdose Reversal project. Given ToxIC's experience in multi-center studies and its well-developed infrastructure, it is well-positioned to provide a nimble response on the part of the medical toxicology community to addressing evolving toxicological threats, drug and chemical toxicosurveillance, and other important medical toxicology priorities.

Keywords Medical Toxicology · Poisoning · Overdose · Surveillance · Epidemiology

Launched with humble beginnings on January 1, 2010, the Toxicology Investigators Consortium (ToxIC) was spawned with the vision that the collective experience of medical toxicologists could be harnessed to do meaningful research, collect systematic data, and to develop a multi-center research consortium. Formed by the first two authors of this Commentary, we were aware that, at the time, opportunities to do meaningful multi-center bedside research in our newly emerging sub-specialty were limited. This was not ideal for medical toxicologists and worse for our patients. A new paradigm for medical toxicology research was needed, and the time was ripe in 2010.

After a survey of medical toxicologists and some back-of-the-envelope calculations, it was determined that even at that time, approximately 15,000 medical toxicology consultations were being done at the bedside annually and that there was enthusiasm for systematic data collection on these patients [1, 2]. If successful, this promised to be a win for our patients as they would ultimately benefit from the research gained from our pooled experience and a triumph for medical toxicologists who will have more opportunities to participate in and lead medical toxicology research projects. When launched on January 1, 2010, four sites were participating, which grew to 29 by the end of the first year, signaling the enthusiasm for the ToxIC concept.

From the time of ToxIC's modest beginnings, the two leads had a bigger vision. In an almost eerily foresightful way, they envisioned future funding from the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA). With resources in hand, it was believed the Core

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Registry would grow and ToxIC would evolve into a multi-faceted, multi-center research consortium.

As ToxIC rolled into its fifteenth year this year, the Core Registry reached the milestone of its one hundred thousandth case. With time, the Core Registry has become a multi-dimensional research tool. As important questions have been identified, the Core Registry has demonstrated its ability to be versatile in the information it garners, and in its ability to collect detailed data on emerging toxicologic threats and critical questions that could best be answered by harnessing the experiential knowledge of the medical toxicology community.

Over the last 15 years, the Core Registry has evolved by deploying a series of focused data collections and sub-registries dealing with topics ranging from vaping to the impact of antidote shortages to surveillance for new and unusual drugs or presentations (Fig. 1). Most recently, the ToxIC Core Registry has launched the CDC-funded medication for opioid use disorder sub-registry which has focused data collection questions on harm reduction interventions for patients that medical toxicologists care for with opioid toxicity or withdrawal. These data collections and studies have been described in relevant publications and in the ToxIC Annual Reports, which have been published in the *Journal of Medical Toxicology* since the first year the ToxIC Core Registry was completed [3–15].

One of the most successful additions to the Core Registry is the North American Snakebite Registry (NASBR). NASBR is a highly detailed prospective study of snakebites treated by medical toxicologists. With data from over 2,000 snakebites to date, NASBR is the most extensive database on snakebites in existence. NASBR publications and abstracts can be found on the ToxIC website: https://www.acmt.net/nasbr/.

The Core Registry continues to be the fundamental bedrock of the ToxIC program and has demonstrated the power of leveraging the medical toxicology community's collective experience and expertise. Yet, the Core Registry's initial successes quickly led to new opportunities for medical toxicologists to do more and better research (Fig. 2).

Because of the volume of prospective, near real-time data being collected in the Core Registry, the FDA recognized ToxIC's utility as a data stream to enlighten issues they were investigating. This led to an FDA contract starting in 2016, allowing the Agency to access the ToxIC Core database to further its mission of assuring drug safety. This initial experience formed the basis for a close, vibrant, and fruitful relationship between ToxIC and the FDA. Within 4 years of starting this important collaboration, a major public health emergency evolved, and because of ToxIC's established relationship with the FDA, they turned to the medical

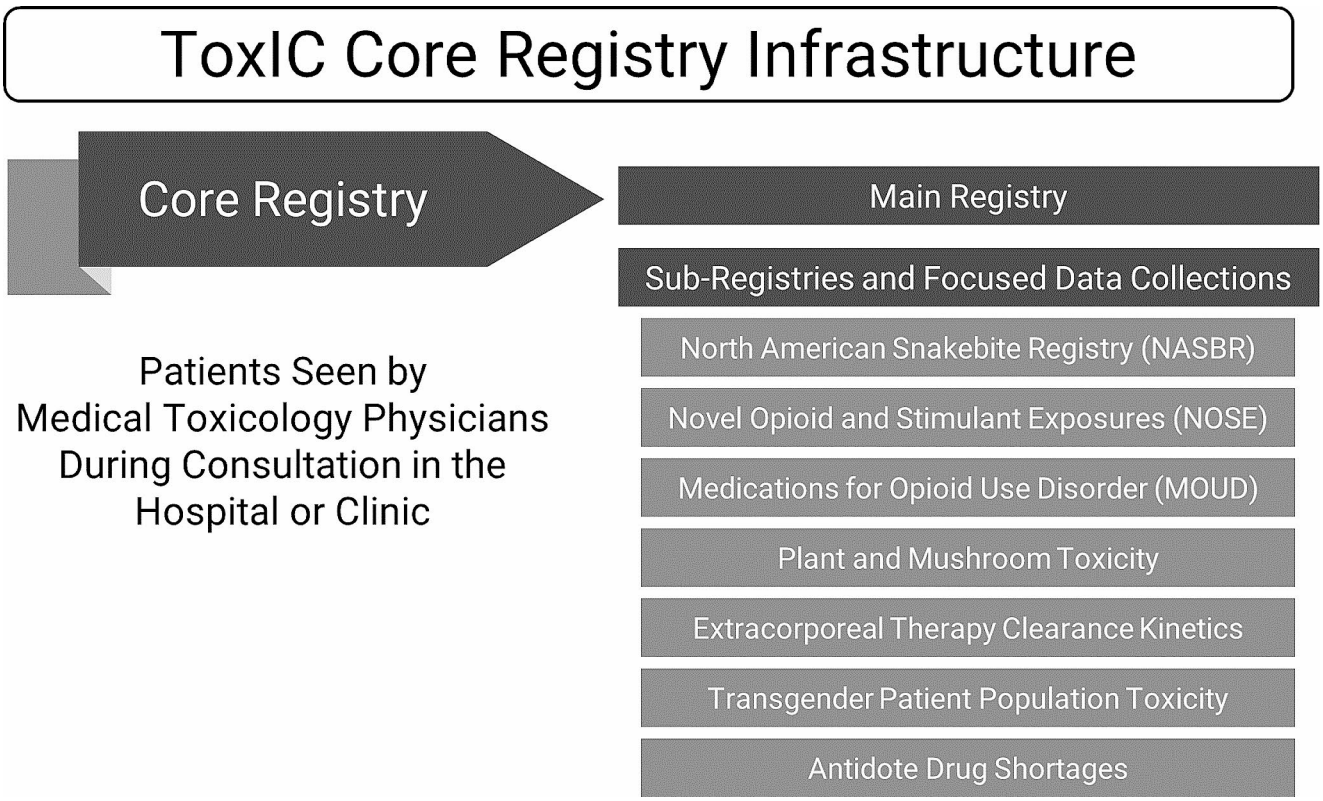

Fig. 1 The Toxicology Investigators Consortium (ToxIC) core registry infrastructure: main registry and sub-registries/focused data collections

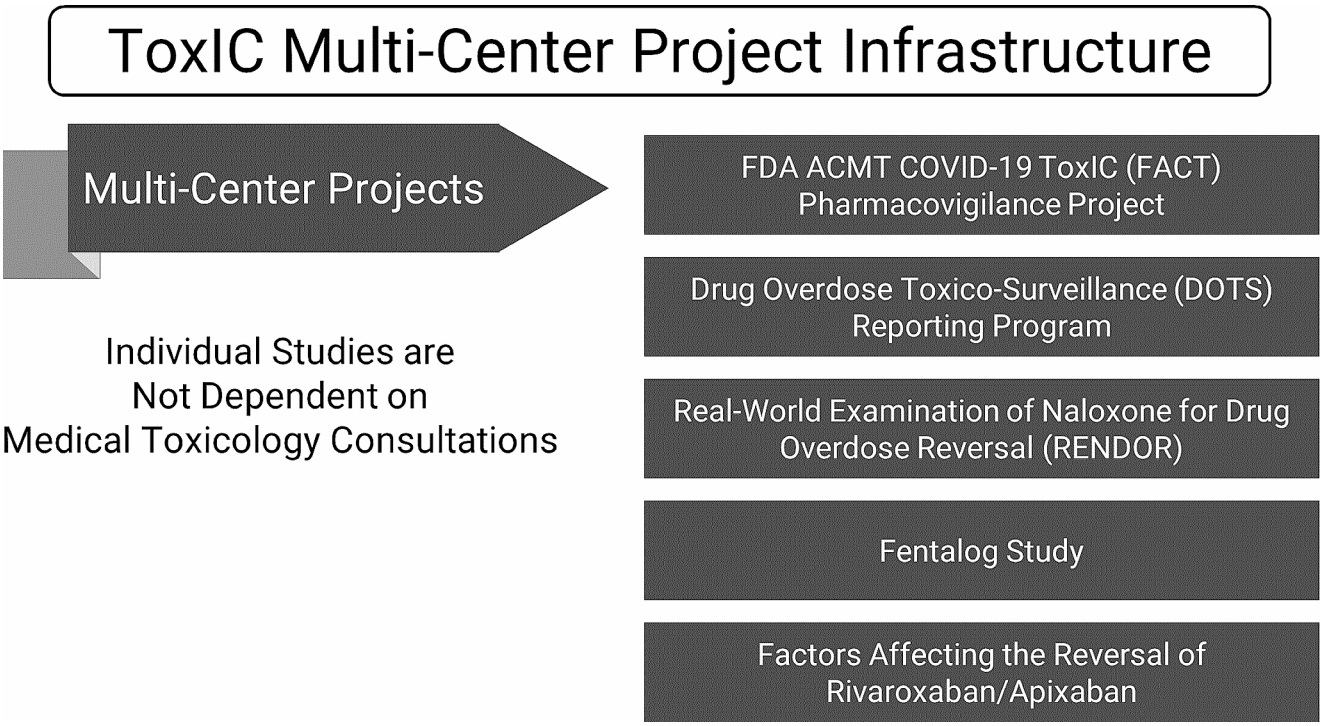

Fig. 2 The Toxicology Investigators Consortium (ToxIC) multi-center project infrastructure

toxicology community for assistance. ToxIC Investigators did not disappoint them.

As the cloud of COVID-19 descended on the United States in 2019, many drugs and other chemical substances were being used off-label to treat patients with little empirical supporting evidence. Even some of the medications approved by the FDA were done so by short-circuiting the usual drug approval process by utilizing Emergency Use Authorizations. Because of this, the potential for iatrogenesis and adverse drug effects loomed heavily on the medical community at large. Medical toxicologists stood at the forefront of these concerns. The FDA, cognizant of the medical toxicology community's nimble facility at data collection through working with the Core Registry, now turned to ToxIC during this public health emergency, and the FDA-ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project was quickly launched. ToxIC's FACT study was able to characterize approximately 1600 adverse drug events related to the treatment or prevention of COVID between 2020 and 2023. All of the sites in this multi-center study were led by medical toxicologists, most of them with an established and demonstrated ability to collect data through their participation in the ToxIC Core Registry. These cases were identified by the medical toxicology site principal investigators working closely with physicians and pharmacists throughout the hospital and some of their outpatient clinics. FACT generated significant publications on adverse events associated with off-label treatment with ivermectin [16] or hydroxychloroquine [17], the use of liver function tests in decisions related to continuation of remdesivir therapy [18], COVID treatment in pregnancy [19], and on other COVID-related toxicologic topics [20].

ToxIC received its first NIH funding in 2013, just 3 years from its inception, from a supplement to an NIH R01 grant on organophosphate countermeasures (principal investigator Steven Bird), investigating chemical threat agents reported to the ToxIC Core Registry. In 2014 ToxIC partnered on an R56 grant (principal investigator Edward Boyer) from the National Institute on Drug Abuse (NIDA) to investigate patients exposed to novel psychoactive agents, such as synthetic cannabinoids, who presented to 10 participating emergency departmentsat ToxIC sites[21]. The same year, Alex Manini was awarded a 5-year R01 from NIDA that studied the cardiovascular complications after overdose using the Core Registry as the data source [22].

As successive waves of the opioid epidemic resulted in increasing death rates, largely due to the recently emerging threats from fentanyl and its analogs, NIDA funded the Fentalog Study, again with Alex Manini as the principal investigator, to investigate the rapidly evolving overdose crisis. When launched in 2020, the Fentalog Study was one of the very few prospective multi-center studies characterizing acute non-fatal opioid toxicity, a characteristic that is still true today [23, 24]. As in all ToxIC studies, and staying true to its original vision, a medical toxicologist principal investigator leads each site in the Fentalog Study. Unlike the Core

Registry, the Fentalog Study is not dependent on medical toxicology consultations. Each patient in the Fentalog Study presented to a site emergency department with a suspected opioid overdose. The Fentalog Study includes comprehensive qualitative blood toxicology testing, which is lacking in traditional surveillance systems on drug overdoses that rely on a chief complaint or discharge diagnosis codes [25]. Waste blood samples from Fentalog patients are sent for comprehensive toxicological testing, relying on the highly sophisticated analytic capabilities of ToxIC's partners at the Center for Forensic Science Research and Education (CFSRE). The Fentalog Study has documented the progressive disappearance of heroin from the illicit drug supply, the increasing use of stimulants, primarily methamphetamine, being used in conjunction with opioids, detected toxicity by the new illicit opioid class of benzimidazoles (or nitazenes), identified novel opioids and stimulants, characterized contaminants such as strychnine and medetomidine as they entered the drug supply, and determined the geographic patterns of adulteration by xylazine and other agents. So far, the Fentalog Study has generated 31 published abstracts presented at national and international meetings and 5 full papers, including ones in *JAMA Network Open* and *Mortality and Morbidity Weekly Reports* [26–30]. A number of others are currently under review or in preparation. More information about the Fentalog Study can be viewed at https://www.acmt.net/fentanyl-analog/.

The diversity of psychoactive substances and potential adulterants and contaminants detected in blood samples from the Fentalog Study patients presenting with apparent opioid overdoses was stunning. The data generated is so unique that the CDC provided supplemental funding to NIDA to increase its toxicological testing capacity. Additionally, the CDC developed an online Fentalog Dashboard to increase the dissemination of Fentalog data [31]. This Dashboard was listed by the Department of Health and Human Services as one of the Biden-Harris Administration's advancements in overdose prevention strategy and new actions to treat addiction and save lives [32].

The Fentalog Study is able to detect substances that are present at the time of an opioid overdose, however it did not answer the reasons why all these substances were present and, because of the qualitative nature of the analytics, how each of these substances relates to the clinical syndromes and responses to treatment being observed. Detailed patient interviews and quantitative drug-level determinations would be necessary to answer these questions. Given this need, and because of the unrelenting frequency of drug-related deaths in the US, now involving both opioids and stimulants, the FDA funded the multi-center Drug Overdose Toxico-Surveillance (DOTS) Reporting Program. Launched in 2023 and led by medical toxicologist investigators at each site, DOTS prospectively incorporates detailed patient interviews, clinical data, and quantitative drug levels on patients with opioid, stimulant, or mixed drug toxicities. The intersection of clinical syndromes, responses to naloxone, patient interviews, and quantitative drug levels allows for a true understanding of the clinical effects of these agents and the syndromes engendered, which would not be possible any other way. The data collected in DOTS can be viewed in the DOTS Digest and CSFRE DOTS quarterly reports (https://www.acmt.net/dots).

Some of the most vexing questions that ToxIC is attempting to assess in both Fentalog and DOTS relate to naloxone administration. Among these questions are the dose of naloxone necessary to achieve adequate ventilation in patients exposed to fentanyl analogs, nitazenes, and other potential mu-opioid receptor agonists; how much is enough without precipitating opioid withdrawal syndromes in patients exposed to these agents; whether there is a relationship between patients' blood drug levels and the amount of naloxone required; how well bystander administered intranasal naloxone works and what complications accrue from its use; and to what degree, if any, is stimulant, toxicity unmasked in patients with an opioid-predominant toxidrome after use of both opioids and stimulants.

Yet, even with comprehensive analytical testing, lessons from DOTS and Fentalog taught us that it was impossible to answer these important naloxone-related questions without knowing the doses and responses when patients received these interventions before they arrived at the hospital, which was frequently the case. Emergency Medical Services (EMS) "run sheets" are difficult to track down, and when found, rarely contain sufficient information about prehospital naloxone administration to answer these questions. Almost no information could be found on run sheets about naloxone administration before EMS arrival at the scene. ToxIC needed individuals participating in the prehospital phase of these patients' arc of care to obtain these data.

Because the FDA had recently approved over-the-counter naloxone, it was very interested in knowing the answer to the questions enumerated above. Once again, they expressed confidence in the medical toxicology communities' ability to collect the relevant information as they awarded ToxIC a new contract for the Real-World Examination of Naloxone for Drug Overdose Reversal (RENDOR) project. Just in the process of being launched in 2024, RENDOR utilizes formalized EMS data collection at four DOTS sites to obtain detailed information on the circumstances, doses, and responses to naloxone administration by bystanders, non-medical first responders such as police or fire, and/or EMS. RENDOR also uniquely provides a glimpse into the usually elusive circumstances of how the patient was found and what was happening at the scene. While these stories

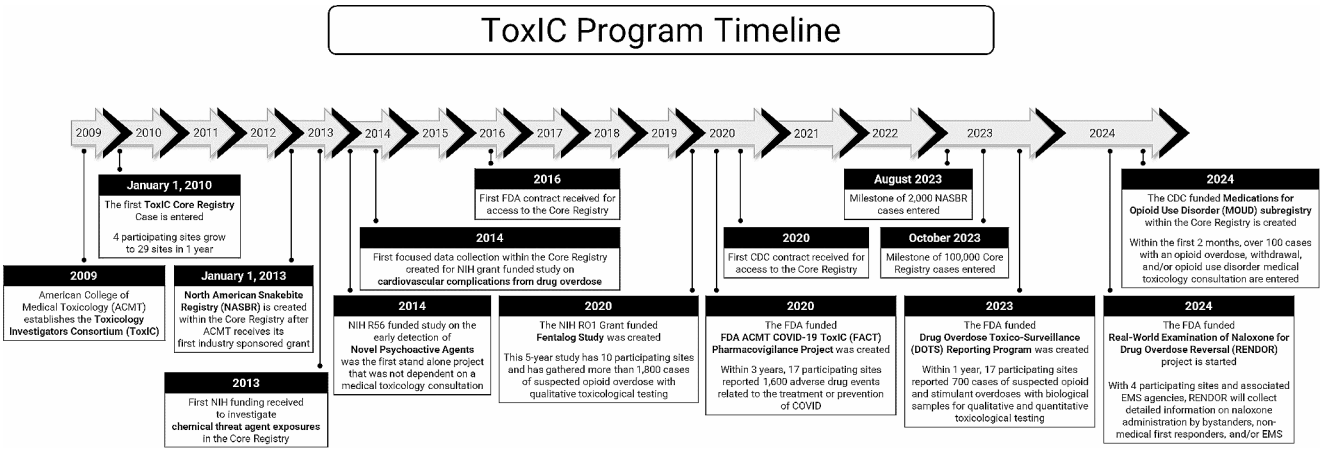

Fig. 3 The Toxicology Investigators Consortium (ToxIC) program timeline

from EMS are often heard in an abbreviated and unstructured fashion when they deliver patients to emergency departments, this information is never systematically collected. RENDOR was designed to provide a lens through which data can be obtained on this usually opaque aspect of opioid toxicity.

Over the years, ToxIC investigators have generated 86 full published papers and 262 published abstracts presented at national and international meetings. There have been 60 different investigators in the first author position of ToxIC full publications alone. The total number of medical toxicologists and fellows-in-training authoring ToxIC papers and abstracts is in the hundreds.

As ToxIC matures into the latter half of its second decade, 45 individual institutions and 53 medical toxicologists act as principal investigators on these various projects. Over $1,740,000 has been distributed to medical toxicologists since 2023. Figure 3 shows a timeline of the evolution of the ToxIC program.

The ToxIC program provides a well-developed research platform with a sophisticated infrastructure that can be used for participation in medical toxicology research and provides opportunities for medical toxicologists and fellows-in-training to produce peer-reviewed papers and abstracts for presentations at major meetings.

There are lessons embedded in this brief history of the ToxIC program. Most importantly, the medical toxicology community is both able and enthusiastic about research that will benefit our patients. Through ToxIC, medical toxicologists have taken the lead in studying the two major drug-related crises that have occurred since its formation: COVID-19 and the proliferation of illicit and dangerous drugs. Given 15 years of experience, sophisticated infrastructure, and well-developed networking capabilities, ToxIC is now well-positioned to provide a nimble response on the part of the medical toxicology community to further evolving toxicological threats, drug and chemical surveillance, and important research questions.

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Declarations

Conflict of Interest None.

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