Ethics and Medical Toxicology Research

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Abstract Optimizing care in medical toxicology necessitates designing and conducting ethical research. Nevertheless, the context of medical toxicology can make clinical research ethically challenging for a variety of reasons: medical toxicology is typified by relative rare conditions; making precise and rapid diagnoses is often fraught with uncertainty; emergent and urgent clinical exigencies make consent difficult or impossible; and some exposures are stigmatized or related to illegal activities that can compromise collecting accurate data from patients. In this paper, we examine some of the ethical issues in medical toxicology research that are especially salient in effort to promote optimal research in the field. The particular issues to be addressed are as follows: (1) rare conditions and orphan agents, (2) randomization and control arms, (3) inclusion and exclusion criteria, (4) outcome measures, (5) consent, (6) confidentiality, (7) registries, (8) oversight, and (9) transparency and reporting. Thinking about

these ethical issues prospectively will help researchers and clinicians appropriately navigate them.

Keywords Ethics · Research ethics · Medical toxicology · Consent

Medical toxicologists have a fiduciary obligation to provide optimal medical care to their patients. As the history of medicine makes clear, clinical practices once thought to be beneficial are often shown to be ineffective at best or harmful at worst when they are subjected to careful investigation. Such observations support calls for data from research across clinical medicine in general and medical toxicology in particular. It is essential that such research be rigorously designed and conducted, which includes paying careful attention to the associated ethical issues.

While there is an established set of criteria regarding what makes research ethical in general [1], the context of medical toxicology can make clinical research ethically challenging for a variety of reasons. First, medical toxicology is typified by relative rare conditions making it difficult to have an adequate sample size and to have these problems be attractive to research sponsors. Second, making precise and rapid diagnoses is often fraught with uncertainty, which can translate into difficulty with meeting inclusion and exclusion criteria for research that are necessary for conducting sound science. Third, emergent and urgent clinical exigencies make consent difficult or impossible raising questions about the ethical acceptability of research. Fourth, some exposures are stigmatized or related to illegal activities that can compromise collecting accurate data from patients and also necessitates using careful measures to protect confidentiality.

In this paper, we examine some of the ethical issues in medical toxicology research that are especially salient in an

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effort to promote optimal research in the field. The particular issues to be addressed are as follows: (1) rare conditions and orphan agents, (2) randomization and control arms, (3) inclusion and exclusion criteria, (4) outcome measures, (5) consent, (6) confidentiality, (7) registries, (8) oversight, and (9) transparency and reporting.

Rare Conditions and Orphan Agents Medical toxicology involves treating an array of rare conditions, making their systematic study difficult. Moreover, rare conditions can be a disincentive to manufacturers to develop and distribute safe and effective therapeutic interventions since the market for such interventions is relatively small in comparison to interventions that aim at treating more common conditions. As an ethical issue, this raises concerns related to justice for those who unfortunately experience devastating, but rare conditions. One mechanism that has been employed to overcome such challenges in the USA by the Food and Drug Administration is to offer “orphan drug status” to particular agents that are expected to be used in less than 200,000 people each year [2]. For example, following open-label observational research of andexanet alfa for factor Xa associated bleeding [3], orphan drug status was granted to the manufacturer [4]. Nevertheless, orphan drug designations may not alone support manufacturing of particular agents and trigger research efforts as has been described for the use of Prussian Blue in the treatment of thallium and cesium poisoning in particular [5] and many antidotes in general [6]. Accordingly, other incentive structures would be welcome to meet clinical needs in such settings.

Randomization and Control Arms Where feasible, randomized, controlled clinical trials should arguably be employed to assess the efficacy and safety of clinical interventions. However, such trials must also be ethically appropriate. A key consideration in determining the ethical acceptability of randomly assigning a research subject to particular arms of a trial is whether clinical equipoise exists. Clinical equipoise describes a state of genuine uncertainty among the expert community about the relative safety and efficacy of alternative treatment arms, regardless of treatment variations [7]. For example, although there appears to be marked practice variation regarding the administration of oral versus intravenous treatment with *N*-acetylcysteine for acetaminophen overdose, clinical equipoise seems to exist [8].

Note that clinical equipoise should exist for each arm of a trial, including active and placebo controls, even for interventions that have been approved for particular uses. This is well-illustrated in the placebo-controlled trial of Crotalidae Polyvalent Immune Fab for North American crotalid (e.g., copperhead and cottonmouth) envenomations [9].

Nonetheless, clinical equipoise alone is not sufficient to justify randomization. Of importance in some clinical settings is the need to preserve decision-making about treatments based on the unique needs of particular patients [10]. For example, even

though it would be appropriate to conduct a properly designed randomized trial of extracorporeal removal versus only medical management for lithium poisoning, certain clinical conditions (e.g., renal failure, hyperkalemia, pulmonary edema) might favor the clinical choice of extracorporeal removal rather than enrolling a particular patient in a trial [11].

Inclusion and Exclusion Criteria Good clinical research is often predicated on having precise inclusion and exclusion criteria. However, medical toxicology is replete with challenges related to diagnostic certainty. For example, it is impossible on initial presentation to emergently identify cyanide poisoning with certainty. The clinician may suspect cyanide based on the clinical scenario and supporting laboratory data (e.g., elevated lactate) but a definitive clinical diagnosis will not be immediately available when decisions about therapy are made [12]. Similarly, although in some settings many lay people can distinguish venomous from nonvenomous snakes, patients with snake envenomation may not be able to identify the specific snake, which may be relevant in determining appropriate treatment [13]. In settings such as these, it is critical that inclusion criteria capture those who are likely to have a particular type of poisoning and would therefore potentially benefit from an intervention, but this must be balanced by the obligation not to expose those who are not poisoned from the possibility of being harmed by unnecessary interventions. As a matter of fairness, it is also important not to inappropriately exclude special populations, such as children and pregnant women, who may benefit from interventions that are being tested.

Outcome Measures Careful consideration needs to focus on the use of appropriate outcome measures. Primary outcome measures ideally concern critical matters such as survival and patient reported quality measures in the long term. However, ascertaining the latter may be more complex for a variety of practical and conceptual reasons, which can make it tempting to use more proximal measures such as drug concentrations, metabolic measures, or even survival to hospital discharge. Unfortunately, such measures may not give a properly robust assessment of an intervention that could diffuse inappropriately into practice. For example, hyperbaric oxygen may rapidly decrease carboxyhemoglobin concentrations and other markers of poisoning but it is unclear if this intervention actually improves long-term neurological outcomes from carbon monoxide poisoning [14]. Similarly, hemodialysis rapidly reduces lithium concentration but it is unclear if the intervention affects long-term outcomes of lithium poisoning [11].

Of particular concern in medical toxicology is the potential confounding of outcomes with withdrawal of care. While it can be ethically appropriate to withdraw care in certain clinical settings where there may be a clear articulation of a patient’s or their surrogate’s preferences to do so, this may have unanticipated implications for the assessment of an

experimental intervention. For example, if mortality or survival to hospital discharge are used as outcome measures, withdrawal of care could plausibly affect this measure even though randomization might be expected to minimize such concerns. Regardless, since the clinical interests of patients should generally override the research interests of investigators, ethically and legally acceptable withdrawal of care should be permitted. Nevertheless, researchers should consider incorporating metrics about withdrawal in research plans.

Consent Informed consent is an established basic ethical and legal requirement for most clinical research. However, obtaining consent is predicated on having adequate decision-making capacity, posing significant challenges to much medical toxicology research due to the very nature of poisoning and often the emergent clinical setting. Nevertheless, wherever possible researchers should seek to obtain consent from patients for research, formally assessing decision-making capacity if it is in question. In some jurisdictions, it is legally permissible to obtain consent for research from patients' legally authorized representatives, but this assumes that the patient is a minor or is incapable of doing so. Further, in the USA, it is possible to use an exemption from the requirement to obtain consent for certain research in the emergency setting [15]. For example, this exemption has been used to conduct research on cardiac arrest and profound shock.

As a related matter, additional complexities are introduced in the context of suicide attempts. While the general default practice for clinical medicine is to treat poisoned suicidal patients under presumed consent, it does not necessarily follow that research interventions would be permissible absent explicit consent. Accordingly, explicit consent for research interventions should be obtained from suicidal patients with adequate decision-making capacity (or their legally authorized representative if they lack capacity).

Confidentiality Upholding confidentiality is a key ethical expectation in most clinical practice and research. The expectation of confidentiality promises to enhance the likelihood that patients will provide truthful information about exposures and behaviors that may be stigmatized or illegal, thereby facilitating good patient care. Accordingly, since the misuse of some substances (e.g., prescription and non-prescription opioids) may be stigmatizing, researchers need to identify means to protect confidentiality, such as not including personally identifiable information from datasets. In addition, it is possible to obtain a Certificate of Confidentiality that is intended to provide protection of research records from subpoena [16].

In contrast to settings where measures to protect confidentiality are introduced in effort to confer protection to patient-participants, additional complexities would expectedly arise where there is reasonable suspicion that certain poisonings were deliberate and intended to harm the patient. Here,

sharing information with appropriate legal authorities is perhaps the best means of ensuring a patient's well-being. Nevertheless, clinical researchers encountering such issues should work closely with patients, their institutions, and authorities to ensure they are managed appropriately.

Registries Registries can help generate important information about particular exposures and their management [17]. The Toxicology Investigators Consortium (ToxIC) registry contains relevant clinical data from consultations performed at participating sites. Information from registries may be especially useful when conditions are rare as well as to help establish the effectiveness of particular interventions in clinical practice following the demonstration of safety and efficacy (and perhaps licensing) in clinical trials. Registries devoted to toxicology may identify use of specialized antidotes and therapies that are not investigated elsewhere [18, 19]. To maximize their potential, registries should employ strict criteria related to data quality and entry. Nonetheless, it is essential to recognize that all such research may be subject to bias in recording and analysis. Just as in clinical research, measures should be taken to protect confidentiality, recognizing that this is complicated by the desire to maintain contact with patients to obtain long-term follow-up information.

Oversight Oversight helps to ensure the proper conduct of research and includes that provided by research ethics committees (or Institutional Review Boards), data monitoring committees (or data and safety monitoring boards), and conflict of interest committees. There is broad recognition of the requirement to have research with human subjects approved by a research ethics committee for this research in general and in medical toxicology research in particular [20]. Research ethics committees are generally charged with ensuring that proposed research is ethically sound and legally permissible. Although research ethics committees conduct an extensive review at the outset of research and determine provisions for consent, they typically conduct continuing review during the life cycle of a trial. The independence of research ethics committees from the investigator and sponsor can provide an important critical distance to help ensure research is appropriately designed.

While all research should have a plan for monitoring emerging data, randomized controlled and multicenter trials frequently use a data monitoring committee for this function. A primary benefit of an independent data monitoring committee is that it can in a non-conflicted manner help interpret emerging data to determine if clinical equipoise has been perturbed by either harm or benefits experienced in one or more treatment arms of a trial. In addition, a data monitoring committee may be able to determine if a trial will be futile and therefore making it appropriate to stop early.

Investigators may be funded by manufacturers of investigational antidotes. Conflict of interest committees are positioned to

review the financial relationships of investigators in a trial to help ensure that these interests do not pose a threat to trial integrity or to participants. Where appropriate, conflict of interest committees may modify consent provisions so that especially conflicted investigators do not themselves obtain consent for a study and/or these interests are disclosed to those who are asked to participate.

Transparency and Reporting As in other fields, research conducted in medical toxicology should be transparently designed and conducted. Transparency is important in promoting public trust in the clinical and research enterprise. Efforts to publicize current research efforts should include listing on clinical trial registries (e.g., www.clinicaltrials.gov). Reporting of research results, regardless of the research outcome is critical. Very simply, results of well-designed research should be disseminated as a means of enhancing scientific understanding. As such, this helps to get potentially safe and effective interventions to patients who need them and can prevent the inadvertent use of well-intentioned interventions that may not be effective.

Concluding Comments Research in medical toxicology promises to advance the care of patients. However, it is essential to prospectively identify and address the ethical challenges that are associated with its design and conduct. Doing so can be facilitated by reviewing the ethics literature on related research efforts. In addition, when research approaches are novel or unique ethical issues are anticipated, researchers should seek advice from their research ethics committees regarding potential ways of addressing these issues in light of current regulations and guidance. In particularly complex research settings, researchers and sponsors should consult with those with expertise in research ethics and regulations. Such approaches will help researchers and clinicians navigate appropriately the ethical issues in medical toxicology research.

Compliance with Ethical Standards

Conflict of Interest Dr. Sugarman is a member of Merck KGaA's Bioethics Advisory Committee and Stem Cell Oversight Committee; a member of Quintile's Ethics Advisory Panel; and has been a consultant to Novartis on a bioethics issue. None of these activities are directly related to the material discussed in this paper. Dr. Stolbach declares that he has no conflicts of interest.

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