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Acute Agitation and the Exception From Informed Consent Requirements



To the Editor:

We read with great interest the article by Klein et al.¹ The editorial by Dickert and Sugarman² accompanying this article argues that Food and Drug Administration regulations concerning the practicability of informed consent in emergency medicine clinical trials lead to ethical ambiguity. We agree that some regulatory restrictions may be at odds with scientific rigor and commend Klein et al for their creative study design.

Dickert and Sugarman² suppose that Klein et al could have proceeded with their original plan to use exception from informed consent by incorporating a feature that would allow patients to prospectively opt out of the study, citing the Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial.³ However, Kelin et al report that the majority of patients treated for agitation and ultimately enrolled in the study were in that condition because of alcohol intoxication. Because the subjects of the IMMEDIATE trial were conceivably coherent at the time of the assent process, as described in the enrollment methods, they could have realistically received information about the study and excluded themselves from research participation if so desired. In contrast, the majority of the patients described in the study by Klein et al experienced acute agitation, likely precluding such understanding and decisions in regard to study participation. Aside from the fact that agitated patients who are uncooperative routinely undergo

sedation to aid in the safe completion of medical screening related to behavioral disturbances, to our knowledge there is not a feasible method of providing an opt-out option to that population, given the primary dysfunction they are being evaluated for.

In their editorial, Dickert and Sugarman² posit that another reason for the Food and Drug Administration's decision to not approve an Investigational New Drug application may have arisen from the position that acute agitation itself is not a life-threatening condition. In punctuating this point, they note that exception from informed consent rules were put in place specifically for acute life-threatening crises such as traumatic brain injury and cardiac arrest. Because agitation is a cardinal presentation rather than a diagnosis, it is often an indicator of either an acute crisis or a worsened chronic condition requiring immediate attention.⁴ We argue that acute agitation is a potentially life-threatening situation, especially in cases of excited delirium, suicidal ideations or attempt, and homicidal behavioral.⁵ In fact, there are several life-threatening conditions that may present as acute agitation, including postictal seizure, metabolic derangement, head trauma, and exposure to environmental toxins. Furthermore, many states, including the ones these authors have practiced in, consider many behavioral disturbances to be life-threatening; hence, the legal ability to detain patients against their will and make them undergo medical stabilization. Although the medications described in the study are not primarily lifesaving, these agents allow physicians and staff to safely perform the legally mandated medical screening, which includes diagnostic studies to exclude medical causes.⁶

We argue that exception from informed consent is appropriate under this interpretation. To advance the discussion, we encourage Klein et al to further elaborate on their exception from informed consent experience with the Food and Drug Administration and institutional review board.

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1. Klein, et al. Intramuscular midazolam, olanzapine, ziprasidone, or haloperidol for treating acute agitation in the emergency department. *Ann Emerg Med.* 2018;72:374-385.
2. Dickert NW, Sugarman J. Ethics and regulatory barriers to research in emergency settings. *Ann Emerg Med.* 2018;72:386-388.
3. Selker HP, Beshansky JR, Sheehan PR, et al. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. *JAMA.* 2012;307:1925-1933.
4. Helman A, Strayer R, Thompson M. Emergency management of the agitated patient. *Emergency Medicine Cases.* Available at: <https://emergencymedicinescases.com/emergency-management-agitated-patient/>. Accessed December 4, 2018.

5. Vilke GM, DeBard ML, Chan TC, et al. Excited delirium syndrome (ExDS): defining based on a review of the literature. *J Emerg Med.* 2012;43:897-905.
6. Zuabi N, Weiss LD, Langdorf MI. Emergency Medical Treatment and Labor Act (EMTALA) 2002-15: review of Office of Inspector General patient dumping settlements. *West J Emerg Med.* 2016;17:245.

In reply:



We appreciate the opportunity to respond to the letter by Wheeler et al¹ in regard to our editorial about ethical and regulatory challenges raised by the study of sedatives to treat acute agitation reported by Klein et al.² We agree with the authors of this letter that, from an ethical perspective, it probably would have been appropriate to have conducted the trial under an exception from informed consent, and we welcome further discussion about why this did not occur. Yet Wheeler et al have 2 concerns with our editorial: we suggest exploration of opt-out or assent options when possible in the conduct of exception from informed consent trials; and we mention that one reason the Food and Drug Administration did not approve the proposed trial as an exception from informed consent study may have been that acute agitation was not considered life threatening.

In regard to the use of opt-out or assent, we do not dispute the assertion that participating in an opt-out or assent process might not be possible for patients who are acutely agitated. In fact, we stated this in our editorial. Our point was not to argue that Klein et al² should have involved agitated patients in these ways. We agree that this was likely not a practical solution in this clinical context. Rather, we believed that it was important to highlight that there is sometimes a possibility for limited involvement of patients in decisions about enrollment, even in trials acceptably approved under exception from informed consent. When such involvement is possible, it is important to consider and to pursue.

In regard to the life-threatening nature of acute agitation, we do not dispute the claims that Wheeler et al make about potential adverse medical consequences of ineffectively managed acute agitation. In contrast, we argue that the determination of whether a condition affects mortality is not ethically relevant to whether exception from informed consent should be acceptable. If the potential risks and benefits of a proposed trial are appropriate and commensurate with background risks of the condition and existing therapy (as is required by other stipulations within the exception from informed consent regulations³), exception from informed consent may be ethically appropriate regardless of whether the condition