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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In reply:

We appreciate the opportunity to respond to the letter by Wheeler et al[1] 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 al[2] 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 regulations[3]), exception from informed consent may be ethically appropriate regardless of whether the condition

likely affects mortality. Our reason for discussing the history of the "life-threatening" requirement was to explain how it came into existence. It was incorporated because the exception from informed consent regulations were primarily designed to facilitate trials in highly mortal conditions such as cardiac arrest and traumatic brain injury. As we suggested in our editorial, we believe that this requirement may have the unintended consequence of making trials such as this one involving acute agitation difficult to approve from a regulatory perspective. Wheeler et al delineate ways in which acute agitation may be considered potentially life threatening; our contention is that neither they nor the investigators should have to do this.

In summary, we agree with the position that this study would have been ethically appropriate to be conducted under an exception from informed consent. Our editorial was not an argument to the contrary but rather an articulation of potential regulatory barriers and areas in which current regulations and ethics may not fully align.

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In reply:

We thank Wheeler et al[1] for their inquiry. We fully agree that the use of exception from informed consent is appropriate and necessary for performing quality agitation research. If we refrain from conducting research on agitation, we are depriving this population of advancements surrounding their care. Wheeler et al requested we elaborate on our experience with the Food and Drug Administration (FDA) and institutional review board.

In 1996, the FDA established criteria for exception from informed consent (21 CFR 50.24) for greater-than-minimal-risk research when informed consent is not possible. With these guidelines, there were finally stringent protections for research on these vulnerable patients who, because of the acuity and nature of their condition, cannot provide meaningful informed consent. In 2005, investigators from our institution sought to perform a randomized, double-blind trial comparing droperidol, ziprasidone, and midazolam for treatment of agitation, using exception from informed consent. Unexpectedly, in their communication with the FDA (through an Investigational New Drug application), they were informed the trial was exempt from needing Investigational New Drug approval, presumably because of the assessment that this was a minimal-risk study.[2] The trial was successfully conducted and is considered a landmark study on agitation treatments.[3]

A decade later, our research group attempted to perform a similar study, focusing on out-of-hospital treatment of agitation with ketamine and haloperidol. After provisional institutional review board approval and community consultation, the Investigational New Drug application was submitted. The FDA again informed us that the study was exempt. This time, however, we pointed out to the FDA that this may be inconsistent with exception from informed consent regulations and requested that the application be rereviewed. They agreed, and then on their review, the application was declined; the FDA claimed that there must be a subgroup of patients with agitation who could provide consent, and therefore exception from informed consent requirements were not met.[4]

In response, during the next several years we conducted multiple investigations exploring this notion. We studied whether agitated patients had capacity to consent, using a standardized capacity tool[5]; whether legally authorized representative consent was feasible[4]; and whether obtaining "preconsent" (rather than prospective consent) could be used.[6] The findings from these studies all clearly demonstrated that meaningful informed consent is not