

Misuse of “Usual Care” in Emergency Care Research: A Call for Adapting Rules Governing Exception from Informed Consent (EFIC) Studies

Macklin and Natanson raise concerns surrounding the misrepresentation of usual care in three critical care studies. (Macklin and Natanson 2019) Emergency care research also yields examples of studies where claims of usual care give rise to ethical concerns. We present two such studies, *A prospective study of ketamine versus haloperidol for severe prehospital agitation (Cole et al. 2016)* and *Intramuscular olanzapine, midazolam, ziprasidone or haloperidol for the treatment of acute agitation in the Emergency Department (Klein et al. 2018)* and suggest how regulations might be adapted to improve quality and oversight.

Both were comparative effectiveness studies that employed a prospective observational design where medications for agitation were rotated on pre-determined timelines. In the Cole et al. prehospital study paramedics administered whichever block of medication was stocked on the ambulance at the time to eligible patients. In the Klein et al. Emergency Department (ED) study patients received medications per-protocol for that block unless they had a known allergy or the treating provider felt a different medication was indicated, “although this was strongly discouraged”. (Klein *et al.* 2018) In both studies the drugs, indication and design were said to reflect usual care of agitation. Such claims are problematic for several reasons.

First, while the drugs evaluated in these studies are used off-label to treat agitation, they are not all approved for this indication. Most concerning was the use of ketamine, a potent anaesthetic used in surgery and in procedures requiring deep sedation. When study drugs are used for an unapproved indication but designated usual care, it should heighten our scrutiny of such claims.

Second, it is doubtful that the settings and protocols in which the drugs were used reflected usual care as understood by Macklin and Natanson (Macklin and Natanson 2019). In the Cole et al.

study, although the system had extensive experience using Ketamine for agitation, there was no evidence to suggest that this treatment protocol was “usual care” outside of this one community. The investigators themselves note that, “data describing its (Ketamine’s) use..., are limited to case report, and case series.” (Cole *et al.* 2016) Like the cases described by Macklin and Natanson, efforts were insufficient to define the existing evidence to an extent that would justify a usual care designation. Similarly, in the Klein et al. ED study, the authors note that the drugs used “represent commonly used standards of care in the United States...” but without citing a single reference. (Klein *et al.* 2018)

Third, it is problematic that the study designs employed were understood as observational. Observational studies report on standard states or processes over time where the variable of interest is not controlled by the investigator. In both emergency care studies, the variable of interest, the medications, were purposefully and systematically controlled by the investigators. When the usual environment is controlled or manipulated in a pre-determined fashion to evaluate an effect, the design is experimental, albeit in this case more aptly quasi-experimental. (Campbell *et al.* 1966)

The problematic elements above were not picked up by oversight under the regulations which were applied. In emergency studies where patients cannot provide informed consent, two sets of regulations may be used; the Waiver of Informed Consent (WIC) Regulations or the Exception from Informed Consent (EFIC) Regulations (Department of Health and Services 1991; US Department of Health and Services 1996) Only one of these, the WIC Regulations, can review and approve studies of non-life-threatening conditions. So too, WIC Regulations only permit studies where procedures are deemed to be no more than minimal risk. By accepting that these studies constituted usual care, the institutional review board (IRB) also accepted that patients would have received these same medications outside of the research context. As such, study medications were understood not to contribute to the risks of the research. This maintained a threshold of minimal risk and allowed the studies to proceed under WIC Regulations. Yet it is unclear why the designation of usual care should

guarantee that minimal risk applies, especially considering the problems we have raised. From an oversight perspective, it is doubtful that the minimal risk assessment functioned effectively and appropriately in these cases. It is therefore uncertain that the usual care designation generated sufficiently robust decision-making for permitting a consent waiver. This suggests that oversight under WIC Regulations may not be appropriate.

In contrast, the EFIC Regulations may provide a better starting point for robust, appropriate oversight. (US Department of Health and Services 1996) Currently, their scope excludes the study of non-life-threatening emergency conditions like agitation (Dickert and Sugarman 2018). Yet in other respects, we suggest the EFIC Regulations stimulate more of the right kinds of considerations pertaining to ethical decision-making in usual care emergency studies. First, investigators and the IRB should be satisfied that: 1) existing science supports the proposed study and investigators have justified why further evidence is needed; and 2) available treatments are unproven or unsatisfactory. Second, assessments of risks are based in what is reasonable rather than what is minimal. This replaces a simple restatement of usual care as minimal with a more in-depth, nuanced risk assessment. Third, there are additional requirements for other “protections” including a data safety monitoring board, as well as consultation with communities which might be targeted by the research.

Community consultation may be a significant check on usual care emergency care studies that propose to limit treatment choices. This occurred in our examples where medications were fixed in blocks and preferences and other medications were discouraged. Limiting choice in a situation where usually providers or patients have the option to express choice preferences is ethically significant and would argue either against medication blocking or against a waiver of consent being appropriate. Consultation in relevant communities may help to raise these issues. The EFIC Regulations therefore could potentially offer more robust oversight of usual care emergency studies.

Klein and Cole appear to have reached similar conclusions. In Klein *et al.*, the investigators preferred to conduct their study under EFIC Regulations and applied to do so. Their application was rejected because agitation was classed non-life-threatening and there was “insufficient evidence” that the subjects could not provide informed consent. (Klein *et al.* 2018) Additionally, in both the Klein and the Cole studies, investigators performed community consultation. This indicates investigators also considered the issues involved to require a more robust process of oversight than provided for under WIC Regulations.

Macklin and Natanson offer recommendations for defining and examining claims of usual care in order to improve research quality and oversight. We offer the following additional considerations for usual care emergency care research. As a first consideration, we join Macklin and Natanson in noting the perennial problem of how we understand usual care. What is usual varies and clearly what is usual is often distinct from what is evidence-based. There can be significant disagreement about what clinicians in good faith usually do and about what the evidence shows and how it is applied. Moreover, what matters for clinical research is that it is close to practice so that the research can be applied. In research which depends heavily on this proximity to practice, we need some systematic method of deciding what is usual. There also needs to be a judgment about the extent to which the evidence base, or lack thereof, should be relevant in this decision. These interrelated but distinct judgments are both relevant to determining when the usual care designation is appropriate.

A second consideration reflects the social and political pressures which suboptimal oversight systems place on clinician-researchers. When oversight structures do not fit, even well-intending researchers that seek to protect subjects and conduct high-quality studies can end up performing ethically suspect research. This has occurred previously in emergency care research and again in our examples. (Biros *et al.* 1998)

We have argued that emergency research which is designated as involving usual care requires improvements in quality and oversight. We have suggested how the EFIC Regulations may yield such improvements; however, some adaptations are in order. First, studies of urgent but non-life-threatening conditions with greater than minimal risk should be eligible for oversight under EFIC. Waiving consent should not depend on whether an emergency condition is life-threatening. Rather it should depend on whether incompetence is a central feature of the condition being studied. Second, within the ethics review process we should encourage reflection on the idea of usual care and the difficulties associated with (i) providing evidence that a practice is 'usual' and (ii) showing that the practice itself is evidence based. Ideally, this would allow researchers and IRB to give reasons and develop conditions under which research designated as involving usual care can be ethically permissible with a waiver of consent. Finally, we should clarify how emergency research oversight under EFIC is justified, lessening its incoherence among investigators and IRBs. Our suggested regulatory adaptations could help address the problems of quality and oversight, enabling high-quality emergency care comparative effectiveness research to go forward while simultaneously enhancing human research protections.

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