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Commentary on Kim and Miller

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In this commentary, Kim and Miller aim to refute what they refer to as the Standard of Care Principle, which they define as the view that studies that randomize between common clinical practices do not "raise significant ethical issues." They are critical of others whom they believe support this "principle," even though this explicit "principle" has not been articulated by those they criticize. Their approach is problematic because it is not clear to what they are objecting, and their labeling the concern as "standard of care" only adds further confusion.[1] We agree with two of the substantive comments in their paper: 1) the social value and clinical validity of research on medical practices should be considered in the review process, and 2) study participants should typically be aware of the purpose of a study and the alternatives to participation. But the tone of their paper conveys a diffuse and vague criticism of others who probably do not hold the view appearing to be the subject of their critique. Further, while there may be important substantive differences between the argument in this paper and other proposals,[2,3] including other papers written by the authors[4] about the rationale for regulatory waivers or alternation of consent and documentation, this paper does little to elucidate those distinctions. The focus on the Standard of Care Principle is distracting and does not advance the exploration of important related issues.

First, the Standard of Care Principle has not been articulated previously in the literature and Kim and Miller do not define it clearly enough to make sense of it. We recommend that further discussions of this issue use greater specificity. It is difficult to know what it means to not "raise significant ethical issues." Consider each of the following claims about the ethical approaches to randomization between common clinical practices:

1. These studies never require IRB review (which would require revision to current regulations).
2. They never require informed consent.
3. Sometimes these studies are minimal risk.
4. Sometimes they can be ethically conducted under a waiver or alteration of informed consent or waiver of documentation of informed consent.

Though Kim and Miller sometimes seem to be concerned about regulatory review (claim 1) the only citation they provide is to a group that has explicitly rejected this claim.[2] Instead, those authors argue for the more nuanced view that the oversight required for research should be tailored to the risks of the research, the expectations of participants and the specifics of the clinical practice being evaluated. In any case, it is not clear that anyone supports this view. It is an impracticable view, since it is unlikely that the required changes

to the current regulatory system are going to take place. Similarly, to the best of our knowledge, no one has defended the view that informed consent is never necessary (claim 2) for such studies. If these two claims are the core of the Standard of Care Principle, then it is doubtful that there is much of a debate, for these are views no one holds.

In contrast, a very significant debate exists if by the Standard of Care Principle Kim and Miller mean to be critical of claims 3 and 4. If Kim and Miller mean to argue that randomization always introduces greater than minimal risk and therefore should not be eligible under any circumstances for waiver or alteration of informed consent or its documentation, they would be articulating a view that is consistent with the most recent draft guidelines issued by OHRP.[1] Unfortunately, if that is the claim that they are trying to make, their reasoning is not sound. In fact, in other publications, Kim and Miller point out that some related trials may be minimal risk and that focused oral disclosure (requiring waivers of documentation and alteration of consent) may be appropriate.[3,4]

To support their criticism in this paper, Kim and Miller cite the BPMedTime study to suggest that the study investigators are wrong to consider this a minimal risk study. There are a number of reasons why this is a poor example to demonstrate their argument that involve details of the proposed trial. Kim and Miller argue that previous studies and an ongoing trial have already demonstrated that taking anti-hypertensive medications at night appears to be superior to taking it only in the morning. While they express skepticism that much will be learned from BPMedTime, they do acknowledge several reasons why the studies in Spain might not be generalized to the U.S. population. The BPMedTime investigators agree that there is some evidence in favor of PM dosing, but it is not definitive. That is why the investigators are not utilizing a standard design. In the study, no patients who currently receive PM dosing are given AM dosing. Instead, the intervention is to randomly move some patients to PM dosing (the intervention arm), while the control arm is strictly observational and patients continue with current usual treatment. For patients in the control arm, there is no difference between what they would receive if they were outside of the trial. While the purpose is to learn if there is a difference in outcomes, it does not follow that there is a risk of harm that is different compared to usual care. It is challenging to believe that patients have increased risk of harm in the observational arm and Kim and Miller seem to hold that there is possible benefit, but no risk, in the interventional arm. Therefore, investigators argue that this is a minimal risk study.

The investigators are not currently requesting that informed consent be waived or altered for the study. The investigators have developed an interactive, on-line consent form and process that they want to utilize as much as possible, making witnesses impracticable. While the investigators do not require waiver of documentation, they might be eligible for such a waiver, as the study is minimal risk and documented consent is not standard for the timing of dosing.

Kim and Miller seem to find fault with the possibility that the informed consent forms (which they have not read) might imply that the study is minimal risk and hence be misleading. We would argue that to state anything other than that the study is minimal risk would be misleading. It is important to disclose the relevant background and the purpose of

the research to participants.[3] The investigators believe that there is some evidence to support the hypothesis that PM dosing for hypertension is likely to be advantageous and Kim and Miller agree. That should be clearly stated in the explanation of the purpose of the research. But the purpose of research is not a risk of the research, particularly in a design such as this one.

In an earlier paper, Kim and Miller argue for what they call an “integrated approach” to consent for such research that would involve clinicians having explicit conversations with patients so they could decide if study participation was acceptable to them. This approach is only feasible in the current regulatory framework for studies that are minimal risk, since it would require a waiver of documentation of consent and an alteration of consent. We support Kim and Miller’s approach in that paper. But it is worth noting that in that paper they seem to endorse the very version of the Standard of Care Principle that they are criticizing here.

In short, in this commentary, Kim and Miller either refute a view that no one holds (that standard of care research never requires oversight or consent) or argue against a view (that randomized comparative effectiveness studies can sometimes be minimal risk and conducted under waiver of documentation or alteration of consent) that they themselves have held previously. Moreover, their example, far from illustrating a greater than minimal risk study, is in fact a minimal risk study (though one whose unusual design make it a poor choice to illustrate the general concepts at play here). Kim and Miller’s primary concern appears to be that pragmatic clinical trials require oversight and attention to the consent process, and therefore should not be considered minimal risk, which might imply oversight and attention to informed consent is not necessary. We agree with Kim and Miller that oversight and attention to consent are important for pragmatic clinical trials. However, we substantively disagree that this study poses more than minimal risk. Equally importantly, the regulatory determination of minimal risk allows the oversight process to utilize innovative consent processes focused on communication and decision-making for participants.

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