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Real Pragmatism, Kids, and the Clinical and Translational Science Award (CTSA)

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The need to involve children in clinical research is clear. Without the inclusion of children in research, pediatric practitioners must rely on data from adult subjects, which often have little relevance in pediatric practice. Indeed, the lack of empirical studies on pediatric-specific therapies and disease states often forces pediatricians to base their therapies on their own personal experiences rather than on published data. The National Institutes of Health (NIH) recognizes that including children in research is essential, and in 1998 released the *NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects*, which requires NIH-funded research to include children unless there are “scientific and ethical reasons not to include them” (1998). The policy further specifies seven accepted justifications for the exclusion of children. Due to this NIH policy, the United States Food and Drug Administration (US FDA) Modernization Act of 1997 (Center for Drug Evaluation and Research 1997), and the 1998 FDA Final Rule (US FDA 1998), there has been increasing pressure and improved opportunities for investigators to enroll children in clinical research.

The Pediatric Oversight Committee (POC) of the Clinical and Translational Science Award (CTSA) consortium was formed in 2006 to facilitate pediatric research across the CTSA consortium. At its first meeting, members determined that variability in institutional review board (IRB) review of pediatric protocols is a major barrier to multi-center pediatric research. This is of particular concern in pediatrics because, with the rarity of many childhood illnesses, it is generally impossible for any single center to recruit sufficient subjects to make meaningful conclusions. Therefore, in pediatrics, we must rely on multi-center studies to produce significant results.

Several POC members presented examples from their own experience and from the experience of colleagues in which variability in IRB review at different sites raised significant barriers to multicenter research. Further, some investigators noted that, on moving to a new institution, their study that had been running for some time at their previous institution was rejected by the IRB at their new institution. Based on these concerns, the POC created the Pediatric Research Ethics Consultation Group (PRECG) in an attempt to improve consistency in IRB review across CTSA sites.

The POC also hosted a web-conference at which IRB members from different sites discussed how their IRB would evaluate the same pediatric protocol. Further, experts from the NIH and the FDA discussed federal perspectives on local IRB review. Finally, a panel of experts from across the United States discussed the findings of the day (the web-conference is archived online and is publicly accessible at:

<http://www.ctsaweb.org/meeting.cfm?year=2007&comID=27#mtgID124> [accessed 14 April 2008]). Several themes developed over the course of the conference illustrating some causes

of IRB variability. Specifically, there was significant variability regarding opinions of which protocols represent a minor risk to individual subjects (such studies are approvable under 45CFR46.404), which procedures constitute a minor increase over minimal risk (which are approvable under 45CFR46.406 under certain circumstances), and whether study subjects have a disorder or condition (one of the necessary criteria for approval under 45CFR46.406).

The PRECG will therefore simultaneously pursue two avenues to improve consistency in IRB review of pediatric protocols. First, the PRECG has invited pediatric investigators across the CTSA consortium to submit their protocols (with the IRB paperwork and responses) that raised problems with disparate IRB reviews at different institutions. The PRECG will review these protocols and IRB responses to determine trends in IRB variability. Until we have a clear idea of the causes of IRB variability, we cannot adequately address the problem.

Second, the PRECG will consult with the research ethics consultants and pediatric investigators at CTSA sites. The purpose of these consultations will be to assist in determining what level of risk a protocol represents, and, for protocols that represent a minor increase over minimal risk and do not hold the prospect for direct benefit to subjects (approvable under 45CFR46.406), the PRECG will assist in determining whether potential subjects have a disorder or condition, which is a necessary criterion for IRB approval. The PRECG will also assist in drafting a section of the IRB packet discussing the study's level of risk and explaining why the investigator and consultants believe that such a determination is appropriate.

Through these two initiatives, the PRECG members hope to diminish variability in IRB review across the CTSA consortium and beyond. Through this process, the PRECG will disseminate information, and IRB members across the US may access this information for use in their own deliberations. The ultimate goal is to facilitate multi-center pediatric research while ensuring adequate protection for individual children.

In the target article, Brendel and Miller (2008) argue for a pragmatist approach to IRB review of protocols. Indeed, their argument lies at the heart of IRB variability. As seen during the POC web-conference, IRB members generally have one of two approaches to protocol review. In one regard, some prefer to develop policies for review standardization; for example, some IRBs have developed lists of procedures that represent minimal risk and a minor increase over minimal risk. In another regard, some advocate for a pragmatist approach where IRB members review each protocol to determine whether it is ethically permissible, and then when a protocol is determined to be permissible, the IRB 'fits' it into the federal regulations. This difference in approach seems to lie at the heart of variability in IRB review. Hopefully, the work of the PRECG will illuminate this issue.

What is imperative, however, is that IRBs make determinations within the framework of the federal regulations. While, as Brendel and Miller (2008) argue, many believe that involving healthy children in research that poses a minor increase over minimal risk may be reasonable, such a step would require either alteration of federal regulations or differential application of the code (whereby IRBs would apply federal regulations only to federally sponsored research and would apply a different set of standards to non-federally funded research). Indeed, others have advocated for amending the federal code to allow such research under a "scrupulous parent" standard (Nelson and Ross 2005). Unless such changes are made, however, it is unreasonable for IRB members to approve studies that fail to comply with federal code even when a pragmatist analysis of the protocol determines that it is ethically permissible.

It should also be noted that if IRB members are given more autonomy in decision-making, there is necessarily more variability in review of protocols. If IRBs use a strict interpretation of the regulations, there is a greater likelihood that different IRBs will make similar decisions for the same protocol, whereas when IRBs move to more loose interpretation, the variability

increases. The current regulations are indeed a pragmatic mix of utilitarian and deontologic approaches. The regulations allow children to be placed at risk with no prospect of direct benefit because such research is necessary to improve the health of children as a class, which follows from utilitarian reasoning. However, placing a child at risk for the benefit of others necessarily uses that child merely as a means to an end, which violates Kant's ([1785] 1993) second formulation of the categorical imperative. Alternatively, because children are considered a vulnerable population (based on children's inability to provide valid and legal informed consent for research participation), the regulations place limits on the amount of risk to which a child may be subjected when there is no prospect of direct benefit. Such restrictions run counter to the overriding principles of utilitarianism since they necessarily restrict research that may create great good for many children while placing only a few children at significant risk. As such, the regulations themselves are a clear example of pragmatism.

While there may be significant benefits to allowing local IRBs greater flexibility in pediatric protocol review, there are also risks. Allowing an IRB the discretion to approve studies based solely on pragmatic reasoning would allow the IRB to approve studies that are ethically supportable even when they do not fall clearly within one of the categories under 45CFR46 subsection D. Alternatively, however, because many IRB members believe that the IRB should not only protect individual human subjects but should also facilitate important research, allowing local IRB members to approve studies based solely on pragmatic reasoning would likely lead to some IRBs approving studies that others would view as ethically impermissible.

Under the currently system, however, there is a mechanism for approval of studies that are important and which the IRB feels may be ethically permissible but which fall outside the federal guidelines. This mechanism, detailed in 45CFR46.407, entails a federal review of the protocol. The 407 review panel may indeed approve a study even when the study does not qualify under 45CFR46.404, 405, or 406 if the panel agrees that the study is ethically permissible. Under such a system, local IRBs may use a pragmatic approach to approve studies under the federal regulations, but only the federal panel may use a pragmatic approach to approve studies that are not approvable by a local IRB. While relying on a federal review panel may delay important research to some extent, such a mechanism limits the probability that an investigator might inadvertently place children at inappropriately elevated levels of risk. While there clearly is a role for pragmatic reasoning in IRB discussions, it is also imperative for IRBs to make decisions consistent with federal regulations. If we believe the regulations do not withstand scrutiny, then we must work to modify the federal code. Merely disregarding regulations is both dangerous and unwise.

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