Research with children presents a formidable “boundary case” for informed consent, demarcating an ethical limit to the consent doctrine. We have even gone so far as to question the very existence of informed consent for pediatric research, suggesting that parental permission is a fundamentally distinct ethical concept [1]. More stringent protection from research risk is provided for children because they are recognized as a vulnerable category of human research subjects. Children without parents (wards of the state) are likely to be even more vulnerable. Widely publicized and ethically controversial research involving this population of vulnerable subjects, such as the hepatitis studies at the Willowbrook State School for “mentally defective persons” from 1956 until 1972 and anti-retroviral trials that used foster children in New York City as research subjects in the more recent past, point to the need for clear and consistent policy in this domain.

The Code of Federal Regulations, Part 46, subpart D describes four categories of research with children that may be approved by institutional review boards (oversight boards charged with maintaining ethical standards in research institutions). They are:

- research not involving greater than minimal risk (category 46.404);
- research involving greater than minimum risk but presenting the prospect of direct benefit to individual subjects (category 46.405);
- research involving greater than minimal risk and no direct benefit to individual subjects (category 46.406);
- research not otherwise approvable which represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (category 46.407) [1, 2].

The regulations provide highly specific guidance with regard to wards of the state who are candidates for categories 406 and 407 research, but are curiously silent about minimal risk research (category 404) and higher risk research with the prospect of direct benefit to the child (category 405). Having consistent guidelines across all four categories is desirable to prevent the exploitation of children who are wards of the state while at the same time allowing ethically sound research to move forward. Research on wards of the state that does not exceed the “minimal risk” threshold is not likely to be controversial, so in this article we focus on research with
wards of the state that may expose children to greater than minimal risk while at the same time presenting the prospect of direct benefit to the child (category 405).

**Greater than Minimal Risk**

In the research category of greater than minimal risk, including more than a minor increase in risk, where there is a prospect of direct benefit, the judgment of investigators, institutional review boards, and parents is typically considered sufficient to protect children from unnecessary risk. Wards of the state often do not have parents who are capable of or available to assess the risk and benefit of research for their children. Writing recently in the *Journal of Pediatrics*, Sumeeta Varma and David Wendler recommend that, when parents are unable or unavailable to protect their child’s interest, independent advocates should be asked to protect the ward’s interest [3]. Such advocates are currently mandated for research categories involving greater than minimal risk with no likely benefit for subjects—406 and 407.

Ideally, advocates should understand the proposed study and be able to place its risks and benefits in the context of the individual child’s needs. It is important to determine the probability and magnitude of both the risks and the benefits of a study when assessing whether the child’s needs are being served by participation. For example, if an investigational drug had a 40 percent likelihood of curing an otherwise fatal pediatric cancer, the benefit would outweigh a 5 percent risk of fatal toxicity. While the probability of the benefit is somewhat low, the magnitude of saving a child’s life is great, and the risk of fatal toxicity is, on balance, acceptable. If a different investigational drug had a 90 percent likelihood of increasing a child’s IQ by 10 points but carried the same 5 percent risk of fatal toxicity to the child, few would argue that the potential benefit outweighed the potential harm. Here, while the probability of benefit is very high, the magnitude of the benefit to the child does not outweigh the risk. An increase of 10 IQ points is not likely to change a child’s quality of life significantly or be worth taking the chance that the child would suffer fatal toxicity. These examples illustrate the need to weigh benefit against risk for any child, but may be especially helpful for individuals who have been legally appointed to serve *in parens patriae* for wards of the state.

Both parents and advocates are expected to complete this risk/benefit analysis prior to enrolling a child in research. While it is reasonable to assume that all parents want to protect their children from excessive risk, this is not always the case. For wards of the state, it is quite possible that they came under government custody precisely because their parents were unable to fulfill this obligation. Varma and Wendler point out that advocates appointed for wards participating in categories 406 and 407 studies are often assigned several cases to oversee [4]. In category 405 studies, where risk and prospect of direct benefit must be balanced for each child, optimal policy would limit the number of children assigned to any single advocate, allowing the advocate to devote sufficient time and consideration to the potential participation of each child in the research.
In sum, advocates should be assigned to provide permission before wards of the state can participate in category 405 research, i.e., research with greater than minimal risk but with the possibility for direct benefit for the individual subject. The advocate should be well versed in the potential risks and benefits of the proposed study and in how the intervention is likely to affect the individual child. The number of cases assigned to advocates should be limited to ensure that a thorough assessment can be made of how risks and benefits will affect each child’s needs. This will allow for more consistent regulation and assure appropriate balancing for “boundary cases” such as wards of the state who are candidates for pediatric research.

References

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