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Research Involving Wards of the State: Protecting Particularly Vulnerable Children

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In 2005, allegations arose that hundreds of children in foster care and state institutions were improperly enrolled in HIV drug trials in the late 1980s and early 1990s.(1) A watchdog group claimed that, “The most vulnerable, disadvantaged children are being exploited by powerful entities and used as guinea pigs as if they were not human beings.”(2) Subsequent coverage by the news media,(3,4) investigation by the Office for Human Research Protections,(5) and a congressional hearing(6) focused on whether the studies followed existing federal regulations for research with children who are wards of the state.(7,8) However, the research ethics literature has said little about the underlying question of when children who are wards of the state should be enrolled in research and what safeguards are needed to protect them.

Current federal regulations mandate additional safeguards, beyond those that apply to all pediatric research, for some research with wards of the state. Although these additional requirements are attentive to the concerns research with wards of the state raises, we argue that they do not go far enough. Society is obligated to ensure the harms wards of the state have already experienced due to parental mistreatment or abandonment are not compounded by further harm from inappropriate clinical research enrollment. This means wards of the state must be appropriately protected from risk and from being unfairly selected to bear burdens in clinical research. To these ends, additional safeguards and modifications to existing guidelines are needed.

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Background

FDA regulations define wards of the state as children who are in the legal custody of the state.(9) Typical reasons for children entering state custody include neglect, abandonment, or abuse by their biological parents.(10) In some cases the legal relationship between wards and their biological parents is severed.(10) In other cases, biological parents retain parental rights and stay involved in decisions affecting their children.(10) Although the majority of wards live in foster family homes, approximately 19% live in institutions or group homes.(11)

The most important protections for children in research are ethical investigators, IRB review, and parental protection. The last protection is diminished or lost for wards of the state, rendering them especially vulnerable. In some cases parents are completely unavailable. Parents of wards who do remain involved in their children's lives have nevertheless been judged to be unreliable protectors of their children's interests, given the history of neglect or mistreatment that brings children into state custody. In addition, parents who have already lost some authority over their children's lives and stand to lose more might feel especially pressured to agree with perceived authority figures, including medical professionals. Hence, when considering research with wards, investigators and IRBs cannot assume that parents can effectively contribute, along with investigators and IRBs, to protecting their child's interests in research. This implies that wards are an especially vulnerable group of research subjects and need additional protections.

The state, via courts, child welfare officials, foster parents, and others strives to protect children whose parents cannot do so, and performs this function well in many situations. These individuals play significant roles in enrolling wards in research. Courts or foster care agency officials generally must give permission for children's research enrollment in addition to or instead of parents.(12,13) However, some state-appointed individuals in these roles have many charges and do not know individual children as well as parents generally do. In 2002, the average caseload for caseworkers in foster care programs was 23 children on a given day.(11) As children enter and exit state custody, caseworkers are responsible for many more children over a longer period of time. This puts wards of the state at increased risk, ex ante, of being inappropriately enrolled in research, compared to children in typical family situations.

There are two senses in which enrolling wards of the state in research could be inappropriate: First, wards as a group could be targeted for use as research subjects because they may be easier to access and control than other children. It is widely argued that the benefits and burdens of research must be fairly distributed,(15,16) and this would place an unfair share of the burdens of research on wards, at least in studies that do not offer direct benefits to subjects. Second, without complete parental involvement, individual wards' interests might not be sufficiently protected in research enrollment decisions. For some pediatric research, parental permission is not required under federal regulations (7), generally because the research is low risk and parental protection is not necessary to protect subjects' rights and welfare but would make the research impracticable. In such cases, extra protections for wards of the state might be unnecessary because diminished parental involvement would not disadvantage wards relative to other subjects. But for the majority of pediatric research, in which parental permission is considered an important and necessary protection, guidelines for research with wards must address these two concerns.

Existing Regulations

Children in general are considered vulnerable research subjects. Federal regulations establish specific protections for research involving and well as limits on the level of risk permitted. IRBs can approve pediatric research only in three risk-benefit categories: minimal risk (category 404), greater than minimal risk but with a prospect of direct benefit (category 405),

and a minor increase over minimal risk without a prospect of direct benefit (category 406). Research that exceeds these risk levels (category 407) can in some cases be approved by special review. Within this framework, research in some risk-benefit categories carries further protections for wards of the state.

Minimal Risk Research

The first category of pediatric research in the federal regulations is research posing no greater than minimal risk (category 404). The regulations define risks as "minimal" if the risks "are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."(19) Current federal regulations do not include any additional protections for wards in research in this category, beyond those that apply to all children (Table).

The lack of additional protections for wards seems reasonable if one assumes no serious harm to participants is possible in research posing minimal risk. However, this assumption is based on a mistaken view of research risks. Research risks are a function of both the likelihood and magnitude of potential harm. Therefore a research procedure posing some chance of serious harm can be classified as minimal risk, if the likelihood of the harm as a result of the procedure is sufficiently low.(20) For example, riding in a car is an activity of daily life for most children, but poses some risk of death. Accordingly, a research procedure posing a risk of death could be categorized as minimal risk under the current definition as long as the chance of death does not exceed the chance of death children face while riding in a car. Even though modifications of the current minimal risk definition have been proposed (20), it is likely that no definition would completely eliminate the possibility of serious harm in "minimal risk" research without greatly impeding the ability to conduct pediatric research, given that individuals may have unforeseen, idiosyncratic responses even to generally safe procedures.

Furthermore, IRBs must categorize the risks of research procedures prospectively, when deciding whether to approve the study in the first place. IRBs therefore must make risk determinations for the population of eligible children. Yet the risks of many procedures vary depending upon which specific children in fact enroll. Some children may be subject to greater than average risk, or may find some potential harms more threatening than most children do. For example, venipuncture presents minimal physical and psychological risks to most children, but some find the procedure prohibitively distressing.

Some of this variation can be addressed by exclusion criteria for easily identified risk factors —for example, excluding children with anemia from studies requiring multiple blood draws. However, IRBs cannot anticipate every possible source of added harm. Ordinarily we rely on parents to be aware of characteristics of their own children that make a study less appropriate for them than for most children. This includes greater physical risks such as allergies, psychological risks such as specific fears, or conflict with the family's or child's values. Parents of wards may not be able to fill this role effectively. The facts that minimal risk procedures can pose some risk of serious harm, and that wards have diminished parental protection, suggest that protections are needed to ensure wards are not involved in minimal risk research without clear justification for their enrollment, and careful consideration of their individual interests.

Research with a Prospect of Direct Benefit

The second category of pediatric research is research posing greater than minimal risk but offering participants a prospect of direct benefit (category 405). Like the minimal risk category, current regulations impose no additional protections, beyond those that apply to all children, for wards in this category of research. This approach has been described as following a "clinical care model,"(21) suggesting that when research offers participants a prospect of direct benefit,

the research can be treated similarly to clinical care in terms of consent and permission. If so, investigators can rely on those who make clinical care decisions for the children, whether the parents, state officials, or combination of the two, without additional research requirements.

IRBs can place a study in this category if it includes an intervention or procedure that may benefit the participating children, such as in a Phase III drug trial. However, these studies, unlike standard medical care, often include additional procedures that do not offer a prospect of direct benefit, such as additional scans or blood draws. Research design also includes features that may conflict with children's interests, such as strict adherence to specific dose levels. These features of research, even when it offers a prospect of direct benefit, raise concern that in the absence of full parental protection wards may be inappropriately exposed to risks of research.

Furthermore, IRBs must determine whether the prospect of direct benefit justifies the risks of research participation before the study begins, thus basing the determination on population characteristics. The potential benefits, like the risks, may be more or less likely to accrue to certain children, or may be more or less important to them. Although we usually look to parents to carefully assess their individual child's interests, that protection is weakened for wards of the state. This suggests the need for particular measures to ensure wards' interests are protected in research with a prospect of direct benefit.

Research with Greater than Minimal Risk and No Prospect of Direct Benefit

The third category of pediatric research is that posing greater than minimal risk and does not offer a prospect of direct benefit (category 406). IRBs may approve research in this category only if it satisfies several additional requirements, including that the risks are at most a 'minor' increase over minimal, the research addresses a condition that affects the subjects, and the experience of participating resembles the subjects' experiences in clinical care. Research that does not satisfy these requirements, typically because the risks are greater than a minor increase over minimal, may be approved only by the Secretary (category 407).

Unlike the previous categories, federal regulations do include special protections for wards of the state in research with greater than minimal risk and no prospect of direct benefit. First, for investigators to enroll wards in research in these categories, the study must either take place in a setting where most subjects are not wards, such as a public school, or be related to the subjects' status as wards. This requirement prevents researchers from conducting research exclusively on wards simply because they might be easily accessed and controlled.

Second, for research in these categories, wards must have an independent advocate who agrees to act in the best interests of the child and is not associated with the research or the guardian organization. One individual may serve as advocate for multiple children. This requirement can be justified as ensuring the interests of individual wards are protected when they are enrolled in research. However, the scope of the advocate's authority is not specified, so it is unclear how the advocate is to perform this function. For example, the regulations do not specify whether advocates simply give advice to researchers or make independent decisions and can veto a ward's enrollment in a study.

Proposal

Enrolling wards of the state in research raises two major concerns: the possibility that an unfair share of the burdens of research might fall on wards, and the need to ensure interests of individual wards are accounted for. These concerns are reflected by the special protections currently required for research in categories 406 and 407. However, these concerns are relevant

to research in all risk-benefit categories, so having special protections only for some categories is misguided. Furthermore, some of the existing protections ought to be strengthened.

Studies That May Enroll Wards

We must ensure wards of the state are not selected as research subjects simply because they may seem easily accessible to researchers and that children are not needlessly exposed to risk. This can be accomplished by restricting the types of studies that enroll wards to those for which wards are scientifically required or from which enrolled children may directly benefit. That is, studies without a prospect of direct benefit should only enroll wards if they are designed to answer important scientific questions that cannot be answered without enrolling wards. Although the current regulations put limits on when wards may be enrolled in research in categories 406 and 407, these restrictions are insufficient, even if applied to all risk-benefit categories.

The Belmont Report states that, “less burdened classes of persons should be called upon first to accept the risks of research, except where the research is directly related to the specific conditions of the [burdened] class involved”.(16) A similar principle is expressed in the Declaration of Helsinki and CIOMS guidelines.(22,23) These documents suggest that investigators should not enroll wards in research that could equally well be conducted with children who are not wards. The federal regulation’s requirement that research unrelated to subjects’ status as wards be conducted in places where the majority of subjects are not wards is not sufficient for this protection. This requirement does not preclude deliberately overrepresenting wards in the population of potential or recruited subjects, which may expose them to an unfair share of research burdens even if wards are not the only enrolled group. Furthermore, the diminished confidence investigators and IRBs can have that wards’ relevant interests are all known and considered in the enrollment process suggests enrolling children who have full parental protection is preferable when possible.

Permitting investigators to enroll wards in research without a prospect of direct benefit only when they demonstrate a scientific necessity for doing so would better address these concerns. When a scientific question cannot be answered without studying wards, their increased vulnerability cannot be avoided by enrolling children who are not wards. This includes research addressing the subjects’ status as wards, which is already permitted under the existing regulations. For example, research the health status of children in foster care must necessarily enroll wards. However, there are also situations where studies that do not specifically address wards would lose important data if wards were excluded. For example, a greater than minimal risk study of the pathophysiology of shaken baby syndrome might not obtain a representative sample of patients without including wards, leading to less valid results. If certain research would not be generalizable to wards if performed entirely on non-wards, then wards as a group would be deprived of the benefit of evidence-based treatments unless the research includes them. Existing regulations seem to prohibit enrolling wards in such studies because the studies do not directly address subjects’ status as wards. However, when there are scientific reasons to enroll wards, and the research is otherwise socially valuable and scientifically valid, it may be justified to include wards, provided individual children receive adequate protection.

IRBs would have to exercise their judgment in determining what constitutes a compelling scientific reason to include wards in research without a prospect of direct benefit. For example, if a study cannot accrue sufficient numbers of healthy children because it requires long clinic visits that most parents find too disruptive to their children’s routines, an IRB may find turning to wards as an accessible population of healthy children is not justified.

What about research that does offer a prospect of direct benefit? There may be good reasons to waive a scientific necessity requirement for some studies with a prospect of direct benefit

(category 405). If the potential benefits of a study are substantial and not available outside research, withholding them from certain children because they are wards of the state seems an unfair distribution of research benefits. Just as with determining what constitutes a scientifically compelling reason to include wards, IRBs would have to exercise judgment on whether a study has a sufficient prospect of benefit to justify including wards on these grounds. If there are convincing data from use of an intervention in adults or related conditions, for example, that suggest the research intervention offers a unique prospect of benefit, the case for including wards in the research would be stronger than if there is truly no reason to believe the research intervention is better than otherwise available care. Wards should have access to research that offers a prospect of direct benefit they could not otherwise obtain, provided there are mechanisms in place to protect their interests.

Protecting the interests of individual wards

Even when wards are included in research for compelling reasons, there must be a robust mechanism to ensure research participation is appropriate for each individual child. Current federal regulations provide such a mechanism for wards in some research categories by requiring the appointment of an independent advocate. Although we argue that this protection should apply to all risk-benefit categories, the existing standards for who can serve as an advocate seem sound. According to current regulations, advocates must be independent of the research and the guardian organization. This is reasonable because the advocate should be free from the conflict of interest of being involved in the research, and should not be part of an organization that has power over the legal fate of the child's family.

Regulations allow one advocate to be appointed for multiple wards in a study. One approach would be for investigators to appoint one individual, such as a respected clinician from the community, as advocate for all wards whose enrollment is considered. If a study is expected to enroll a large number of wards, multiple advocates may need to be appointed. Because advocates appointed this way would need to be reimbursed, their independence may not be absolute. However, there are several measure that would maximize the independence of these advocates. Advocates should be reimbursed based on the time spent or number of potential subjects screened, not subjects enrolled, providing no financial incentive to approve enrollment of the screened wards. IRBs could have oversight of investigator-appointed advocates and the ability to remove advocates with conflicts of interest.

Current regulations state that advocates must act in the best interests of the child. Understood strictly, this appears to preclude wards' participation in research that presents any risk or burden, however small, but lacks a prospect of direct benefit. This reading would effectively rule out much research that requires wards to answer important questions but does not offer a prospect of direct benefit, such as studies of the health status of children in foster care. This seems unreasonable in light of the need to conduct research to improve children's health, including specifically addressing the needs of wards. A more reasonable understanding of the advocate's responsibility is to ensure, given that an IRB has determined that a study's risks are minimal or at most a minor increase over minimal for the population of potential subjects, that the study is not unusually risky for or otherwise against the interests of an individual child from that population.

Existing regulations do not specify the actions advocates may take. Several steps may be important to carrying out the role of advocate: First, advocates should become familiar with the research, especially its risks and the demands it places on subjects and their caregivers in general. Second, advocates should consult with the child's day-to-day caregivers and with parents and the child if possible, to understand how participation would influence the particular child's life and interests. Third, advocates should consider the child's entire medical history, not only inclusion/exclusion criteria of the study, and situational factors that might influence

the study's appropriateness for the child. For example, the medical setting itself may be particularly frightening for some children who have not experienced routine medical care or have been abused,(24) and this potential for psychological harm should be considered.

Existing regulations also do not specify the extent of the advocate's authority. In order to effectively protect wards, advocates' assessments should carry considerable weight. An initial assessment should be done before the child enters the study, as well as ongoing oversight if the study follows children over time. Advocates should be able to veto enrollment of a ward of the state in a research study. If the advocate's later assessments determine that staying in the study is against the child's interests, the child ought to be withdrawn. It is particularly important to have an individual continuously responsible for monitoring how a ward fares in the study if the child's foster parents or caseworkers change while the child is enrolled.

Objections and Implications

One possible objection to requiring special protections for wards of the state in research is that it assumes researchers are inclined to act unethically. This objection could be applied to regulations aimed at protecting any human research subjects, not only wards of the state. We acknowledge that the vast majority of researchers aim to act ethically. The purpose of requiring specific steps to be taken before enrolling wards of the state in research is to ensure that the unique issues arising in this group are attended to, and that investigators and IRBs can turn to established guidelines to address them effectively.

There may also be concern that our proposal would hinder important research if applied in the context of some existing state and local regulations. Individual states and localities have rules about research with children who are wards of the state. At the time of the controversial pediatric HIV drug trials, New York City's Human Resources Administration conducted a multilevel review of all trials in which wards might be enrolled, in addition to the usual IRB review.(25) In some states, wards may not be enrolled in clinical research at all.(14) Others have no standing policies but may impose various requirements in an ad hoc manner.(14) Some of these policies are felt to be unduly burdensome to both researchers and wards who might benefit from research participation,(26,27) in which case adding the restrictions we propose could make a bad situation worse. But our proposal could instead serve as a middle ground and replace some existing local requirements. The set of protections that we propose would hopefully provide needed safeguards while not blocking important research or access to potential medical benefits.

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Table

Requirements for Research with Wards of the State

Category	Current U.S. Regulations	Proposed Requirements
Minimal risk (404)	No additional requirements*	**1** Research must require wards for scientific reasons (including research related to subjects' status as wards) **2** Independent advocate with authority to veto enrollment
Prospect direct benefit (405)	No additional requirements*	Independent advocate with authority to veto enrollment
Minor increase over minimal risk (406)	**1** Research must be related to subjects' status as wards, or in a setting where most subjects are not wards **2** Independent advocate	**1** Research must require wards for scientific reasons (including research related to subjects' status as wards) **2** Independent advocate with authority to veto enrollment
Research not approvable by an IRB (407)	**1** Research must be related to subjects' status as wards, or in a setting where most subjects are not wards **2** Independent advocate	**1** Research must require wards for scientific reasons (including research related to subjects' status as wards) **2** Independent advocate with authority to veto enrollment

[#] No additional requirements beyond those which apply to all research with children