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Ethical issues in early-intervention clinical trials involving minors at risk for schizophrenia

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Abstract

Early-intervention clinical trials involving persons at risk for schizophrenia raise a variety of ethical issues. These issues range from some of the most general questions of ethical theory and research ethics to some very specific pragmatic questions about optimal procedures for protecting subjects. Giving special attention to minor subjects (and adult subjects lacking decision-making capacity), this paper aims to provide an overview of some leading ethical issues and concerns as well as a rights-based framework and several concrete suggestions for addressing these issues and concerns. © 2001 Elsevier Science B.V. All rights reserved.

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In recent years, psychiatric research has increasingly captivated public attention, both because of the great promise of much of this research and because of a greater awareness of associated ethical issues. Improving our ability to help mentally ill persons requires research involving human subjects, yet those subjects represent a group whose humanity combines with special vulnerabilities to justify heightened ethical concern about their treatment. When psychiatric research involves minors as subjects, the case for careful ethical scrutiny is increased because minors generally lack the decision-making capacity that grounds the right to make self-regarding decisions about medical care and participation in research. Further complexity is added when the potential subjects are minors *who may or may not* have a particular mental illness or a predisposition for a mental illness, whose treatment, prevention, or underlying pathophysiological basis is under investigation.

Because it addresses ethical issues in early-intervention clinical trials involving minors at risk for schizophrenia (e.g. Yung et al., 1998; McGlashan, 1996; Wyatt and Henter, 1998), the present paper will confront this full level of ethical complexity. The issues raised by such research range from some of the most general questions of ethical theory and research ethics to some very specific pragmatic questions about optimal procedures for protecting subjects. The goal of this paper is to provide an overview of some leading ethical issues and concerns as well as a framework and several concrete suggestions for addressing them.

1. Goals, rights, and protection from harm

In considering the clinical trials in question,

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one point that is beyond dispute is that the goal — to ameliorate or possibly prevent a terrible disease — is enormously important. But what, morally, follows from this important goal?

Some may think that it follows that potential research subjects have an *obligation* to participate in research. But the doctrine of informed consent, including accepted norms for proxy consent (as discussed below), suggests that subjects clearly have a right *not* to participate in research. Moreover, those who elect to participate as subjects have a right *to adequate protection from harm*. With that in mind, one might think that because the research in question is so important, the goal of ameliorating or preventing some dread disease is properly *balanced* against the rights of research subjects (e.g. Appelbaum, 1997). Now, the metaphor of balancing suggests that a sufficient gain with respect to the goal would justify some compromising of patients' rights. As we will see, however, such a claim indicates confusion about the nature of moral rights.

A similar, if subtler, error is committed when people speak of some research as *necessary* (or *needed*), not in relation to some goal ('If we are to achieve such and such, then we must do this research,' which makes perfect sense), but simply necessary (e.g. Vitiello et al., 1999; DeRenzo, 1994). To say some research is necessary is to say, first, that it is extremely important and second, that its importance justifies conducting the research. But what if the research cannot be conducted without violating people's rights? To say that some research is necessary, without any qualification, suggests that it is so important that it should be conducted *regardless* of whether people's rights are respected in the process. But reasonable people are likely to doubt any research is that important. Someone who disagreed with my claim might doubt that individuals *have* any moral rights (e.g. Frey, 1980). Then again, if one doubts moral rights, one might also doubt the moral importance of any goals, such as pursuing the research in question. But then, there would be no basis for saying the importance of the research justifies using human subjects in the first place. At the very least, someone who was skeptical about moral rights but *not* about the moral importance of research (e.g. Frey, 1980) would bear the burden of justifying such selective moral skepticism.

This paper assumes both that the goals of promising research are important and that human beings, including research subjects, have certain rights. These assumptions are in keeping with considered moral judgments about how people should treat one another and with all major codes of research ethics since World War II. Since the concept of a moral right, which is sometimes applied carelessly, is central to this paper, it is worthwhile to clarify what it *means* to say someone has a moral right. It means that the individual is morally *entitled* to the 'object' of the right, say, not to be killed or not to be forced to participate in research. If you have a right to *X*, then *X* is your *due* as a matter of justice. (Whether, in addition to such negative rights, there are positive rights, such as to be provided with food, shelter, or health care, is somewhat more controversial, but the issue of positive rights is not central to this paper.) Rights, we may say, are *justified claims made on behalf of particular individuals* (Feinberg, 1970).

One might reply that while rights are important, so are goals like research progress, suggesting the appropriateness of balancing the two moral concerns (Appelbaum, 1997). But, in protecting vital interests of an individual, rights must generally resist claims of utility or overall benefit to society; otherwise, the tide of appeals to utility will erode the protections that rights are supposed to provide, stripping rights of any distinctive function. Rights, properly understood, *trump* considerations of utility (Dworkin, 1977). That is, rights set limits to the pursuit of goals, even the most important goals. We should pursue important goals very vigorously, but we should not take paths that violate people's rights. In the research arena, this means that a subject's rights must be respected, even if respecting them is inconvenient or expensive, and even if some important research is impeded. To use Kantian language, research subjects may not be used as *mere means* to societal ends (Kant, 1981; Advisory Committee on Human Radiation Experiments, 1995).

As stated earlier, subjects have a right to adequate protection from harm. But how should this right be more concretely specified in the case of minors, who (with rare exceptions) are legally incompetent, or others who are legally incompetent, lack decision-making capacity, or both? (For the sake of

convenience, the term 'incompetent' will hereafter be used to characterize all such subjects.)

2. Specifying the subject's right to be protected from harm

I suggest that, in addressing this question, we recognize that two guidelines merit our respect and more or less cohere with each other. First, there is the US Regulations (or risk-benefit) approach, as stated in the Common Rule, a set of regulations adopted independently by 17 federal agencies. Roughly, the Common Rule states that a minor may be enrolled if the study poses *minimal risk*, or offers *the prospect of direct medical benefit and an acceptable risk-benefit ratio*, to the subject. Moreover, wherever the subject can assent, his or her assent is necessary. Under some conditions, a study posing a *minor increase over minimal risk* and no prospect of direct medical benefit is acceptable (45 Code of Federal Regulations 46, Subpt. D; 34 CFR 97, Subpt. D (1998)). (Although the regulations in question specify minors, we may extend the approach to incompetent adults to whom the best-interests standard applies, as explained below.)

What counts as minimal risk and as direct medical benefit? The Common Rule states that a study presents minimal risk if 'the probability and magnitude of harm or discomfort anticipated in the research are not greater… than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests' (45 CFR 46.102(i) (1998)). One unresolved issue is whether we should compare the risk presented by a study with those ordinarily encountered in the daily life of, say, a person with bipolar disorder (where the study concerns that disease) or in the daily life of a person of normal health. As for *direct* medical benefits, a relatively immediate health improvement would clearly qualify, whereas mere contact with a health professional would probably count as an indirect benefit.

The second guideline stems from a hierarchy of decision-making standards, ultimately justified by the fundamental values of patient (or subject) self-determination and well-being, which represents a point of virtual consensus in bioethics (e.g. President's Commission, 1983). This consensus view holds roughly the following with respect to patients and prospective research subjects. For those who are competent, their *informed consent* is needed for them to be properly enrolled in a study. For those who are presently incompetent but were previously competent, the *substituted judgment* standard is to be applied, if possible. According to this standard, an individual may be enrolled in the study only if available evidence suggests that he or she would have wanted to be enrolled; that is, the prospective subject, when competent, would have agreed to being enrolled in the present circumstances of incompetence. Here, one is still trying to respect the individual's autonomy, but one has to project from values and preferences expressed during a period of competence to the present circumstances of incompetence. An advance directive can be especially helpful for these purposes. Finally, in the case of persons who have never been competent, or whose wishes while competent are entirely unknown, we have no baseline of autonomy from which to project a substituted judgment, so we must revert to the *best-interests* standard. This is the standard that applies to the minor prospective subjects of the early-intervention trials. (For ease of reference, I will refer only to minors, although similar points apply to those incompetent adults for whom no substituted judgment is possible.) According to the present guideline, we must ask whether participation in a given study is compatible with the minor's best interests, considering the degree of risk and any prospects for benefit.

Some may question whether this hierarchy of decision-making standards, whose paradigm application is in the clinical context, fully applies in the research setting. In particular, one may think it is overly stringent to require that minor subjects' *best* interests be served. Then again, the best-interests standard is commonly accepted for application to the research setting, for example, by the National Institute of Mental Health (Shore and Hyman, 1999), the National Bioethics Advisory Commission (NBAC, 1998), and several prominent bioethicists (e.g. Brock, 1994). Moreover, the best-interests standard has been widely accepted, legally and morally, as a way of articulating the responsibility of parents towards their children, and not only in biomedical settings (Beauchamp and Childress, 1994). Perhaps,

the concern that this standard seems too stringent rests on a very literal reading of 'best interests', according to which one must pursue *a perfect maximization* of the minor's interests. This does seem too stringent as an understanding of parental (and proxy) responsibility, apparently precluding the imposition of *any* unnecessary risks, although I do not understand best interests in this rigorous, maximizing way. A possible solution is to understand the best-interests standard as requiring that parents protect and promote the child's *essential* interests, eliminating the associations of perfect welfare maximization while retaining a plausible connection to what we reasonably expect from parents (Robert Wachbroit, personal communication). Hereafter, references to best interests may be understood in this way.

Importantly, the US Regulations approach and the best-interests standard more or less cohere with one another. Where a study poses only minimal risk, or the prospect of direct benefit and a reasonable risk-benefit ratio for the subject, participation seems compatible with the subject's best interests. I have doubts that studies that pose more than minimal risk (perhaps even a minor increase over it) and no significant prospect for benefiting the subject are really compatible with his or her best interests. In any case, we are in a position to state, at least roughly, the content of the minor subject's right to be adequately protected from harm: *The minor subject has a right not to be enrolled in any study that fails to meet the best-interests standard.*

Ultimately, it is up to a minor's parents (or legal guardian) to make such best-interests judgments. But for parents even to be presented with the option of enrolling a minor in a study, it must be reasonable to think participation *might* be in the child's best interests. The Principal Investigator and Institutional Review Board, and perhaps also peer reviewers and any external funding agency, have an obligation to consider in good faith whether it might be in a child's best interests to enroll.

3. Clinical equipoise, risks, and benefits

Might it be in the best interests of minors at risk for schizophrenia to participate in early-intervention trials? That depends on the study design. In some of these clinical trials, there is a placebo arm (although subjects in both arms receive psychotherapy). Whether such a study design is ethically defensible may be addressed in terms of *clinical equipoise*, a state of genuine uncertainty within the clinical community regarding the comparative therapeutic merits of each arm in a trial (Freedman, 1987). In placebo-controlled studies, the two arms feature a comparison between a medication and placebo. For our purposes, then, the crucial question is whether there is clinical equipoise between the study's two arms, taking into account not only efficacy, but also toxicity, any stigma attached to participating, and other risks.

Suppose that clinicians with the relevant expertise agree that being in the treatment (medication) arm is preferable for those subjects who are 'on the path to' schizophrenia. The medication is believed to be at least somewhat effective and associated side effects and risks are not so bad as to negate its advantages. Then, for these individuals, randomization to the placebo arm would seem significantly disadvantageous and therefore contrary to their best interests; although all subjects receive helpful psychotherapy, it would be better for these subjects to receive the medication as well. The study we have imagined, according to this reasoning, is not in clinical equipoise and apparently violates the best-interests standard for at least some potential subjects.

Alternatively, suppose there is a state of clinical equipoise regarding treatment versus placebo. Consider now 'false positives,' subjects who are not on the path to schizophrenia. If they are randomized to the treatment arm, they may experience certain side effects (such as lethargy, serious weight gain, perhaps even irreversible tardive dyskinesia) and undergo certain risks (such as those of emotional distress and of being labeled with a disorder they do not have). For false positives, then, at first glance it seems doubtful that participating in the study can be in their best interests.

On the other hand, maybe it is erroneous to think about best interests from the perspective of someone who is already *assumed* to be a 'true positive' or a false positive. We might instead consider the perspective of someone who displays what *appear* to be prodromal symptoms and otherwise meets eligibility criteria for an early-intervention trial. No one knows

for certain whether he or she is on the path to schizophrenia. Is it in this ambiguous individual's interests to be randomized to the treatment arm, in view of the apparent effectiveness of early intervention and despite the possibility of being a false positive? If the expert clinical community agrees that it is, then clinical equipoise is lacking.

The Yale early-intervention trial headed by Thomas McGlashan, which is funded by the drug company Lilly, provides an interesting test case (McGlashan, 1996). As a double-blinded, placebo-controlled study, it seeks a high degree of scientific rigor in testing the efficacy of early intervention with anti-psychotic medication. All subjects receive supportive psychotherapy. McGlashan and colleagues have attempted to minimize side effects by using relatively low doses of newer, less toxic neuroleptics for a limited time period (one year); they have also been careful to minimize risks of self-stigmatization. Some of McGlashan's remarks suggest that he believes early intervention to be effective, more than compensating for the associated risks (McGlashan, 1996), implying that randomization to the placebo arm is contrary to a subject's best interests. On the other hand, clinical equipoise is disrupted only if the broader expert community concurs.

As noted by Schaffner and McGorry (2001) in this issue, the Yale study was recently under investigation by the US Office for Human Research Protections (formerly the Office for Protection from Research Risks (OPRR)) following complaints from Citizens for Responsible Care and Research. Among the group's complaints was the charge that the trial posed more than minimal risk to subjects while offering them no prospect for benefit. While agreeing that there is more than minimal risk, considering the side effects of the medication used in the treatment arm, the investigators countered that (1) all subjects receive the benefits of careful monitoring and stress-management psychotherapy and (2) subjects in the treatment arm are hypothesized to receive the benefits of avoiding conversion to psychosis and treatment for their current symptoms.

Rebuttal (2), however, seems partly misleading. Based on published data from this and other studies using similar enrollment criteria, only about 35% of those meeting enrollment criteria are likely to convert to psychosis (without the drug treatment) in the year during which they would be in the study (e.g. McGorry et al., 2001)). (McGlashan now asserts a much higher percentage (Schaffner and McGorry, 2001) but no revised estimate has been published or widely accepted.) If that is correct, then about 65% are false positives who do not receive this benefit. Moreover, even those who receive the trial drug convert to psychosis no less than 10% of the time (a rate that was found at six months by McGorry et al. (2001)). This suggests that at most 25% of those in the treatment arm receive the major benefit of avoiding conversion to psychosis. Perhaps some who do convert to psychosis also receive a partial benefit of *alleviated* symptoms. Meanwhile, those in the treatment arm are likely to experience side-effects from the medication (while the false positives among them may incur the stigma of a mental illness they do not have). It is not self-evident that the benefits listed in rebuttal (2) outweigh the risks. (Cornblatt et al. (2001) raise similar concerns about false positives.)

Rebuttal (1) raises the issue of how much indirect benefits should count in calculating benefits to subjects. Certainly the Yale investigators are right that monitoring and psychotherapy are benefits. Psychotherapy can be helpful to all subjects while monitoring permits very rapid detection of, and treatment for, those who convert to psychosis. But, in a study of the efficacy of neuroleptics, monitoring is clearly an indirect benefit and, arguably, psychotherapy is as well. How much importance should be assigned to indirect benefits?

One possible view is that 'benefits are benefits,' so indirect benefits should be given *full* weight. The opposite view is to give them *no* weight, out of fear that some researchers will count such factors as 'relief from boredom' as a significant benefit to institutionalized persons (as if an impoverished institution formed a moral baseline) or will count 'the satisfaction of serving humanity' (where this is a speculative attribution) as a major benefit. Meanwhile, a reasonable middle position is taken by NBAC, which asserts that 'an indirect benefit may be acknowledged, but should not be assigned as heavy a weight as direct medical benefit in the IRB review and discussions with prospective subjects and their representatives' (NBAC, 1998, p. 45).

Even if we assume that psychotherapy is, like

monitoring of subjects, only an indirect benefit, assigning these indirect benefits some weight and adding the direct benefits that will accrue to a minority of the subjects in the treatment arm may very well compensate for the risks mentioned above. But this debatable matter warrants further ethical discussion.

In general, there is some room for reasonable disagreement about the benefits and risks attending particular studies, and about the weight to be assigned to indirect benefits. Researchers and their institutions must consider such matters conscientiously before a study is approved. Where minor subjects are involved, if deliberation over these factors concludes that study participation is inconsistent with their best interests, the study is ethically indefensible from the standpoint taken in this essay. In that case, the study should either be redesigned so that it can meet the best-interests standard or it should be rejected.

4. Practical problems that pose challenges to adequate protection of subjects

There is good reason to doubt that subjects, whether competent or incompetent, are consistently well protected in psychiatric research and other areas of human research. In recent years there have been several media reports of psychiatric clinical trials in which subjects' rights were apparently violated (e.g. Kong, 1998a,b,c; Kong, 1999a,b). Cases in which rights violations led to the *harming* of subjects include several experiments, finally terminated by the federal government, at a Veterans Affairs medical center in Los Angeles (Kong, 1999b) and a psychosis-inducing study at the Mount Sinai School of Medicine in New York (Kong, 1999a). (Of course, it would be a fundamental conceptual error to assume that where there is no demonstrated harm, there is no ethical failure.) Moreover, in the area of gene therapy research a University of Pennsylvania study, whose multiple violations included a highly misleading consent form and, arguably, excessive risks, caused the death of a volunteer who was not acutely ill (Weiss and Nelson, 2000; Weiss, 2000).

In at least one psychiatric study, tragedy resulted from rights violations. In schizophrenia research conducted at the University of California Los Angeles, numerous patients, after receiving beneficial neuroleptics, experienced severe relapse due to long-term withdrawal of their medication, in accordance with the study design. One patient, who was unable to regain the level of functioning he enjoyed before neuroleptics were withdrawn, complained that the investigators refused to remedicate him for months even as his parents repeatedly beseeched them to help their increasingly psychotic son (Wilwerth, 1993; OPRR, 1994, Attachment M). Another patient expressed suicidal ideation more than once, yet no UCLA staff member notified his family or sought involuntary commitment for his protection (OPRR, 1994, Attachments M and N). He committed suicide. The OPRR reviewed complaints from these two patients' families but never conducted a site visit. (Regarding conflicts of interest, it should be noted that OPRR, which, before it became the Office for Human Research Protections, was part of the National Institutes of Health (NIH), consulted with the National Institutes of Mental Health (NIMH), also part of NIH, about the appropriateness of a study design that guaranteed that many subjects would relapse — and that NIMH had funded the UCLA research in question.) In its report, which is likely to strike any impartial reader as very gentle toward UCLA, OPRR concluded that among UCLA's failings was, quite significantly, a consent form that made *informed* consent impossible by inadequately describing the research procedures, greatly understating the risks of relapse, and failing to mention alternative courses of treatment that might benefit prospective subjects (OPRR, 1994). It is doubtful that all of the subjects who experienced the harm of prolonged, severe relapse would have entered the study had they been adequately informed of its risks and of available alternatives; indeed, of the two subjects mentioned above, the one who survived said he would not have entered had he been adequately informed while the family of the deceased subject asserted the same of him (OPRR, 1994, Attachments M and N).

These and other sources of information (e.g. Shamoo, 1997; Rothman and Michels, 1994; Karlawish and Sachs, 1997) suggest that the current system for protecting subjects is not fully satisfactory, although, again, the problem is hardly limited to psychiatric research. At least four practical problems

pose significant challenges to adequately protecting the subjects of psychiatric research.

First, researchers and their institutions have significant *conflicts of interest*, which include both moral and nonmoral dimensions. As representatives of biomedicine, researchers and institutions are charged with the responsibility of protecting subjects' welfare and, where subjects are competent, respecting their autonomy. Conflicting with this interest is, first, another moral interest, that of advancing science and helping future patients. Because of what they do professionally, researchers can be expected to have a general bias in favor of advancing science. In terms of ethical theory, this bias favors societal utility over individual subjects' rights. In addition to this moral conflict of interest, researchers and institutions have a nonmoral (not an immoral) interest creating a conflict with their charge to protect subjects: the interest in greater funding and prestige. This is very familiar, but it must not be ignored.

A second factor posing a challenge to adequate patient protection has been called 'the therapeutic misconception'. This term refers to a pronounced tendency on the part of many potential subjects to believe, despite receiving information to the contrary, that participation in research will be in their therapeutic interests (Appelbaum et al., 1987). In placebo trials, for example, persons laboring under the therapeutic misconception will not process the point that there is an even chance that they will receive a placebo. Even if the study meets the ethical requirement of clinical equipoise, in which case there's no clear advantage to being in either study arm, a subject may mistakenly believe that he or she will undoubtedly receive a well-established therapy. This phenomenon poses a serious challenge to genuine informed consent, underscoring how much more is involved than mere disclosure and the signing of a form. In the case of minor subjects, the challenge involves parents or other proxies representing the minors' interests.

A third practical challenge to adequate subject protection is the special vulnerability of persons suffering from, or at risk for, major mental illness and the vulnerability of their families. Persons with schizophrenia, for example, are likely to be desperate to ameliorate its effects. Those who know that they are at risk are likely to be frightened about the possibilities. And families that include members who are mentally ill or at risk are likely to be distressed and possibly quite desperate. For individuals who are institutionalized and therefore deeply dependent on the goodwill of staff, concerns about displeasing biomedical professionals may be very considerable. For patients who arrive at emergency rooms with symptoms of mental illness, vulnerabilities associated with such illness are compounded by those associated with emergencies. (Some research teams recruit from ERs (Hall, 1999).) But it is common knowledge that such emotional states as desperation, fear, and distress are not autonomy enhancing. Of course, vulnerabilities occur in many contexts and do not automatically preclude meaningful informed consent on the part of subjects or their proxies. But where vulnerabilities can be expected to exist, they must be taken into account realistically.

A fourth practical problem is *the growing influence of pharmaceutical companies in the conduct of research*. Increasingly, psychiatric research is funded by drug companies (Hall, 1999). For example, the Yale study discussed above is funded by Lilly. This is a matter of concern because the *raison d'etre* of a business is a nonmoral (again, not immoral) goal: to maximize profits. Of course, businesses want to avoid lawsuits, and bad publicity, but the bottom line of business is so different in kind from the humanistic concerns of rigorous subject protection that the funding sources of clinical trials should not be ignored. Apparently, some drug companies have introduced admirable innovations into their study review process, such as the use of independent consent monitors (David Shore, personal communication). Still, drug companies' relentless pursuit of profits and their penchant for secrecy provoke legitimate ethical concerns.

5. Possible safeguards to ensure adequate subject protection

In view of these challenges to adequate subject protection, what safeguards should be recommended? First, while recognizing that implementation may be difficult, I recommend the use of independent consent monitors where prospective subjects (or, in the case of minors, their proxies) have questionable capacity and

trials pose more than minimal risk. The monitors should be independent of the research institution and any funding agencies in order to minimize or eliminate conflicts of interest. Their job would be to ensure that consent meets the conditions of meaningful informed consent, including capacity, adequate comprehension, and voluntariness. Second, I suggest that IRB membership routinely include ethicists and, if at all possible, persons who represent the disease population. Ethicists will often raise questions and offer arguments that other professionals will not. Meanwhile, as stressed by the National Alliance of the Mentally Ill, representatives of the disease population have an experiential perspective that should not be neglected (Hall, 1999). Moreover, they have a vital stake in *both* research progress *and* adequate protections. Third, research institutions should do whatever it takes to provide close monitoring of subjects during a study, to protect their welfare and ensure that their continued participation is voluntary. Additionally, there should be significant social supports for subjects and their families, who should be offered user-friendly information about existing services that can help them. Where feasible, they should be presented with opportunities to become connected with programs for which they are eligible. (While early-intervention trials typically offer some social supports, the TIPS study in Stavanger, Norway and the EPPIC study in Melbourne, Australia are especially exemplary.) Finally, I suggest that investigators, IRB members, and others involved in study design and review *regularly* ask these questions: (1) Are the best interests of eligible minors really served if they enter the study?; (2) Would I want my most beloved family member (if similarly situated) to enter?; and (3) Would I mind the study being accurately described on the front page of *The Washington Post*?

6. Outstanding issue: are exceptions to the best-interests standard defensible?

Above it was argued that, in interpreting the minor subject's right to be protected from harm, two promising approaches, the best-interests standard and the US Regulations approach, more or less cohere with one another. But the US Regulations approach permits, in some circumstances, research that presents more than minimal risk (they refer to 'a minor increment over minimal risk') but no prospect of direct medical benefit. Presumably, this category includes some research in which there is *no* significant prospect for benefit, direct or indirect, while presenting more than minimal risk. It may be overly optimistic to assert that participating in such research is compatible with the minor subject's best interests. Arguably, enrolling the minor would disadvantage him or her in a nontrivial way, raising concerns that he or she is being used as a mere means to societal utility. If participating in such a trial *is* contrary to the subject's best interests, might it be justified anyway, especially if the study is especially promising and important, say, in providing basic knowledge about schizophrenia or ways of treating or preventing it?

As explained earlier, rights serve as trumps to considerations of utility. They are not just moral claims to be balanced against utility. Still, from the standpoint of ethical theory, rights can serve this function of protecting vital interests even if there are *occasional* circumstances in which they are overridden. Here, however, we have to take into account not just whether sound moral reasoning sometimes justifies overriding rights, but also the practical consequences of policies that endorse exceptions to rights. As soon as one takes the ethical-theoretical issue to the rough ground of real people making decisions in the face of real-life pressures, one must take seriously the practical problems that pose challenges to adequate subject protection, and the recent rights violations, some of which have resulted in harm (as discussed above).

In view of these practical factors, my working hypothesis is that studies posing more than minimal risk but no significant prospect for benefitting the minor subject should be considered by an entity like the Special Standing Panel recommended by NBAC (NBAC, 1998). This panel would be independent of NIH and other research institutions, so as to eliminate conflict of interest. It would also feature a cross-disciplinary expertise that would include ethics and would not be so dominated by the interests and perspectives of researchers as is now generally the case on IRBs. While creating additional bureaucracy is not desirable, other things equal, other things are *not* equal given legitimate concerns about subject protection and the situation we are contemplating, in which the best interests of subjects who are incapable

of giving informed consent may well be compromised. Recognizing that approval and implementation of this proposal could take years, however, I do not recommend a moratorium on presently approved categories of research in the meantime.

7. Conclusion

Ethics and prudence might be more mutually supporting than they appear at first glance. Like society as a whole, the research community has a profound stake in biomedical progress. But society's mandate to pursue progress depends on a well-deserved trust in the professionals and institutions at the helm of research, a trust that has been shaky in recent years. In my view, safeguards that are somewhat burdensome but correctly perceived to be ethically necessary should increase public trust and, quite possibly, enhance enrollment for studies.

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