

# VULNERABILITY IN RESEARCH SUBJECTS: A BIOETHICAL TAXONOMY

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The concept of vulnerability appears to have been grandfathered into the lexicon, lore, and literature of research ethics without undergoing stringent certification. And yet the need for some such notion has long been appreciated. More than 50 years ago, reflecting on the ethical implications of the Nazi medical experiments, the authors of the Nuremberg Code emphasized the necessity of the subject's informed consent, too hastily ruling out, as it quickly became apparent, medical research on children and those with cognitive impairments.

In the United States, widely studied episodes such as Willowbrook,<sup>1</sup> the Brooklyn Jewish Chronic Disease Hospital Case,<sup>2</sup> and the Tuskegee Syphilis Study<sup>3</sup> provoked debates that eventually gave birth to our current methods for ensuring the ethical conduct of research. But despite the remarkable circumstances of the subjects involved in those studies—institutionalized children, hospitalized elderly, and impoverished and poorly educated black Alabama males—it is not much of an exaggeration to say that in the minds of many investigators the paradigmatic research subject remains more or less a mature, respectable, moderately well-educated, clearthinking, literate, self-supporting U.S. citizen in good standing—that is, a man who could understand a 12-page consent form and act intelligently on the basis of its contents. While I shall assume in what follows both that the existing guidelines are sufficient to deal ethically with the paradigmatic research subject, and, further, that all those standard protections are reliably in place, the vulnerable research subject nonetheless requires ethical consideration going beyond that baseline.

More recently, in the wake of the Nuremberg Code's shortcomings, systematic attention has been accorded to a motley collection of vulnerable subpopulations. In 1979, for example, the seminal *Belmont Report*<sup>4</sup> briefly considered children, the institutionalized mentally ill, and prisoners, mentioning dependency and compromised capacity for consent as representative hallmarks of vulnerability. There was no effort to be comprehensive. The more recent Federal Regulations on the Protection of Human Subjects (45 CFR 46) implement the requirement that Institutional Review Boards (IRBs) take into account the “special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons” (46–111). Criteria for vulnerability are not discussed although subparts are included with supplementary regulations for some of these groups. Finally, the *Final Report* of the Advisory Committee on Human Radiation Experiments,<sup>5</sup> after reviewing patterns of unethical misconduct in military research, recommended special protections for enlistees.

Though this recent subpopulation focus is an improvement over earlier approaches, it is surely reasonable to register comparable concerns when contemplating research on, for example, drug abusers, the desperately ill, Ugandan women, illegal aliens, the impoverished homeless, women in the process of miscarrying, psychology undergraduates, and the elderly in the early stages of dementia. Though commentators may speak as if there were something common to these disparate groups, it is not now clear what that characteristic (or that set of characteristics) is. And even if such criteria were articulated, one would surely want to know what it was about

those features that made those who possess them “vulnerable.” Finally, it is not generically apparent what researchers should do when confronted with a vulnerable subject. These are some shortcomings of the current subpopulation focus.

Regrettably, the term “vulnerable” too often gets played as a bioethical trump card, summarily tossed on the table in the course of debate, sometimes with the stern admonition that it would not be decent to exploit such subjects. Given the absence of agreed-upon standards for identifying and responding to vulnerability, such a move too often serves as a conversation-stopper, abruptly ending dialogue rather than furthering it. It may be possible to do better.

The aim of this paper is, broadly, to provide a needed overview and analysis of the concept of vulnerability and, narrowly, to develop a useful taxonomy. I am here challenging the current subpopulation focus that is evident both in the writings on such research and in the efforts to draft subparts for each designated group. I am arguing that the current conceptualization be supplemented or supplanted by something like the analytical approach that I will set out here. My aim is to tease out and consider circumstances that directly signal the vulnerabilities researchers should take into account. In a list that is intended to be exhaustively applicable to research subjects, six discrete types of vulnerability will be distinguished—cognitive, juridic, deferential, medical, allocational, and infrastructural. If the listed subpopulations are groups deemed to be vulnerable, the six circumstances described here are intended to represent the ethically relevant features that bespeak vulnerability, not only in the designated subpopulations but in other groups as well.

Each of these vulnerabilities is conceived, not as a flashing red light ordering researchers to stop, but rather as a cautionary signal, calling for proper safeguards. Accordingly, having ascertained that a candidate-subject (C-S) is vulnerable in one or more of those discrete ways, researchers would then be required 1) to conduct further inquiries and, if necessary 2) to implement compensating measures in the design of the protocol as a condition for proceeding. While some examples of these measures are sketched or referenced, it is not possible to set out here, much less resolve, all of the pertinent ethical problems. Rather the general aim is to provide a needed map of the conceptual geography, one that offers usable guidance while organizing and sharpening issues that might be fruitfully engaged later. First, however, as a prerequisite to understanding vulnerability, one must reflect on the Nuremberg Code’s foundational concern: the concept of consent.

## **Consent as an Ethical Power**

Consent is usefully understood as an ethical power: something we do with words. Philosophers have found it remarkable—even “magical”—that we have the ability, merely by intoning the proper words under the right circumstances, to alter the systems of obligations and permissions that envelope us.<sup>6</sup> Ordinarily it is a wrong—even a criminal offense—for you to remove my lawnmower from its place in my garage. But if you ask, “Can I take your lawnmower?” and I reply, “You can take my lawnmower,” an action that would have been wrong thereby becomes—Lo!—one that is unexceptional. Merely in saying, “You can take my lawnmower,” I can bring it about that you can take my lawnmower. In giving permission, an act can become permitted.

Note that consent does not always effect permissibility. If I say you can take my neighbor’s lawnmower, it may not be permissible for you to take it. And if I consent to your killing me, you would not thereby be permitted to do so. That some deed is okay with me does not always mean it is okay.

Notwithstanding the occasional misfire, this amazing ability to give or withhold permission constitutes a critically important ethical power. The connections between a contextually appropriate utterance, its dramatic effect on the permissibility of action, and the various circumstances that can impair that connection, causing a misfire: these three elements constitute the focus of the present study. Accordingly, we can define the vulnerabilities that concern us as those special circumstances of the C-S that call into question the efficacy of consent in effecting the permissibility of research. Despite the presence of consent and the standard baseline protections, vulnerability, in conjunction with other circumstances, can occasion a misfire. Absent compensating measures, it may still be impermissible to conduct research.

We can conceive ourselves as surrounded by a zone of privacy the boundaries of which are, characteristically and for the most part, subject to our will. Though the zone's dimensions vary with law and culture, our capacity to exercise sovereign authority over such domains as physical property, certain categories of personal information, our immediate physical environs, our body, our intellectual creations, and so on, is reasonably conceived to be constitutive of a developed sense of self, at least in part.<sup>7</sup> Boundary crossings—physical touching is a ready example—characteristically require an antecedent consent. In the most dramatic case, an act of sexual intercourse is, absent consent, the crime of rape. It is, I think, fair to say that, since the ascendancy of research ethics as a loose body of theory and doctrine, both of which are broadly coupled with implementing organizations (IRBs and national and international agencies), there has emerged a near global appreciation of the relevance of that ethical power in the context of research on human subjects. The entitlement not to be treated as a laboratory animal may be as close as humanity has come to a genuinely secured human right. Before moving on, it will be helpful to mark a potential confusion involving two types of consent. The consent that is of importance here—I have called it *gratuitive consent* elsewhere<sup>8</sup>—constitutes a giving of permission. In consenting, something not permitted may become permitted. But there is a different type of consent that generates obligations. In consenting to the terms of a contract, for example, both parties typically assume reciprocal obligations. Having agreed to terms, you may come to have an obligation to mow my lawn, and I may come to have an obligation to pay you. For the purposes of the present inquiry, the consent pertinent to research ethics is not assumed to encompass this second type consent—we can call it *contractive consent*. Notwithstanding the difference, investigators have sometimes fixated on the separate question of what their research subjects owe to them: strict adherence to a protocol's requirements, for example. My concern here is, rather, with the C-S expressed willingness to be studied as part of a scientific investigation and with the efficacy of that consent in granting permission. I am setting aside questions regarding the duties of the subject following consent.

## **Vulnerability and Biomedical Research**

The concept of vulnerability points in two directions. By definition, it is a distinctive precariousness in the condition of the subject: a state of being laid open or especially exposed to something injurious or otherwise undesirable. A vulnerability is, so to speak, an avenue of attack. But, in the second place and in the contexts where we use the term, we are characteristically mindful of certain others who are disposed to capitalize on such weakness, exploiting open avenues of attack—intentionally or negligently—and taking unfair advantage to the subject's detriment. The wrongfulness of using others in this way, selfishly and unfairly—Kant would say “merely as a means”—characteristically grounds humanity's severe condemnation of research on unconsenting subjects.

To avoid confusion, it is important to mark the difference between the everyday sense of “vulnerability” and the special use pertinent to the context of human research. Consider, for example, the distinctive vulnerability of blind people: they are characteristically less able to protect themselves, and, accordingly, it is easy for wrongdoers to victimize them in certain ways. But this vulnerability is unlikely to be of consequence in the context of most research. Investigators are not lurking out there, waiting to pounce upon and exploit the sightless. Notwithstanding the vulnerabilities of many handicapped persons, the absence of a common capacity does not in itself signal a need for special precaution on the part of researchers. The vulnerabilities that concern us here are only those that call into question the efficacy of consent in effecting permissibility. A person who is plainly vulnerable in the everyday sense may not be a vulnerable research subject. Our focus is on the sense of the term pertinent in the research context.

A second ambiguity may also be a source of confusion. While we can, for example, speak of men as vulnerable to testicular cancer, we are talking about a type of harm that only affects males: we are not referring to a way of being peculiarly laid open to that harm. Being male is not a way of being especially exposed to testicular cancer: it is a precondition for having it. On the other hand, weakened immune systems make people vulnerable to infection. Lacking normal protection, they are at heightened risk. It would perhaps be less confusing to say that males are generically susceptible to testicular cancer, meaning merely that the disease is a harm only they can suffer. Vulnerability, conversely, connotes unusual exposure to some type of injury, and, accordingly, I shall

reserve the term exclusively to describe conditions that heighten the risk of harm. Thus, while only a pregnant woman may lose her fetus, she is not, on that account alone, a vulnerable research subject. When a research protocol heightens the risk of this loss, investigators would surely have to disclose that to her, but she would still not be a vulnerable research subject as we are using these terms. However, assuming both that she will carry the fetus to term and that the protocol can cause fetal malformations, then, depending on one's metaphysics, one could describe as vulnerable either the fetus or the person it will become. Notwithstanding the pregnant woman's informed consent, research might still be impermissible.

A usable analysis of vulnerability will serve at least three purposes. In the first place it will provide a checklist of circumstances that, along with other conditions, can invalidate the permissibility of research. Each of these circumstances generates its own problems. Is it possible, researchers will want to know, to conduct ethically responsible research on these subjects notwithstanding their vulnerability? A usable analysis of vulnerability would have to suggest responses to that question. In the second place, it will provide an intellectual basis for treating a subpopulation as vulnerable and—equally important—for determining, generically, what specific supplementary measures are called for in the light of their vulnerabilities. And, finally, it will provide a basis for a warranted finding that some researcher has, knowingly or negligently, taken unfair advantage of vulnerable research subjects. Though discussion of the range of corrective responses to such misdeeds would also take us beyond the scope of this paper, the setting of standards, in the nature of the case, provides researchers with usable guidelines for the responsible crafting of protocols even as it generates a basis for criticism, condemnation, and discipline following a showing that there has been a serious breach of those same standards.

Foreshadowing the analysis that follows, each of the six types of vulnerability is distinguished by a positive response to a unique question. Summarizing, these are as follows:

Cognitive: Does the C-S have the capacity to deliberate about and decide whether or not to participate in the study?

Juridic: Is the C-S liable to the authority of others who may have an independent interest in that participation?

Deferential: Is the C-S given to patterns of deferential behavior that may mask an underlying unwillingness to participate?

Medical: Has the C-S been selected, in part, because he or she has a serious health-related condition for which there are no satisfactory remedies?

Allocational: Is the C-S seriously lacking in important social goods that will be provided as a consequence of his or her participation in research?

Infrastructural: Does the political, organizational, economic, and social context of the research setting possess the integrity and resources needed to manage the study?

It is important, in the discussion that follows, to be mindful that participation as a subject in medical research generates benefits as well as risks. Well-designed studies produce knowledge that can help similarly situated patients. But, more important, where there are no satisfactory treatments, participation in a clinical trial may be a patient's best chance. For example, during the early trials of antiretrovirals for HIV infection, prisoners justly complained that the existing protective rules were barring their access to the only treatments offering a hope of benefit. As has been observed, it would be toweringly wrong to let sailors drown solely because the available life rafts had not been approved by the Coast Guard. We need to be exquisitely careful not to allow a misguided solicitude to load further and unjust disadvantages upon the shoulders of those who are already disproportionately burdened.

### **Cognitive Vulnerability**

Lawyers make a useful distinction between arm's length relationships and the much closer ties fiduciaries have with their clients. The former is exemplified in the purchase of a used car. While sellers may not lie (or create a misleading impression by, say, setting back the odometer), neither are they bound to disclose all the pertinent information they have. Buyers are thrown upon their own resources. Fiduciaries, on the other hand, have to take their client's interests as primary, working to reduce, as much as possible, the knowledge differential that

marks that distinctive type of cooperation. Where a critical choice must be made, an ethical attorney must ensure that the client fully understands what is at stake. The lawyer's objective is that, regardless of what happens, the client will continue to acknowledge ownership of the decision. Here they must become educators, intelligibly conveying a usable sense of the situation, explaining all the options, and—especially—setting out the risks and possible benefits attaching to each option. With respect to the consent of the C-S, the traditional requirement of informed consent points in the direction of the fiduciary model. The burden on the researcher is not merely to state the pertinent facts, but to ensure they have been appreciated.

Of the six types of vulnerability catalogued here, cognitive limitations are the most familiar. The researcher must ask, “Does the C-S have the capacity to deliberate about and decide whether or not to participate in the study?” Circumstances that suggest the presence of this type of vulnerability would include some degree of immaturity, dementia, certain types of mental illness, and mental retardation. But educational deficits and unfamiliarity with the language may also play a role. Also included would be C-Ss who cannot be sufficiently informed and/or who cannot complete effective deliberation within the available timeframe. For example, some years ago I interviewed patients and clinicians involved in an early trial of tocolytic treatment for preterm labor. At the time the standard treatment was ethyl alcohol. While this could arrest uterine contractions briefly, it was plainly not a satisfactory treatment. Pregnant women brought to the hospital in the process of miscarrying had to make a decision about a complex clinical trial without the time to learn all that was involved or to deliberate effectively. Even apart from the time problem, the C-Ss were in the midst of crisis and not in what educators would describe as a teachable moment. The conception of a cognitive limitation that is commended here is intended to apply to situations like these as well as to the other more familiar cases. Vulnerability is present precisely because the measures ordinarily taken to ensure that the C-Ss are adequately informed will not do in the face of such circumstances.

It would take us too far afield to set out a comprehensive review of the measures researchers might take to address cognitive limitations. We are familiar enough with most of the standard strategies: plain-language consent forms, advance directives (where incapacity is anticipated), supplementary educational measures, and the proper use of surrogates and advocates.

### **Juridic Vulnerability**

Juridic vulnerability calls attention to the formal authority relationships that often characterize social structures. The most striking examples are prisons and the military, where wardens and officers have legal authority over prisoners and enlistees. But the category also includes children under the authority of their parents, psychology students subordinated to their college professors, institutionalized persons (including institutionalized children and their parents) subject to the authority of custodians, and certain third-world woman who may be legally subject to their husbands. Related issues can arise when the C-Ss are engaged in illicit activities. This catalogue is not exhaustive.

In these cases researchers must ask, “Is the C-S liable to the authority of others who may have an independent interest in that participation?” The worry is that the “consent” of the C-S might be merely a reflection of the wishes of those in authority. This distinctive vulnerability—the juridic fact of their subordination to the authority of another—can call into question the validity of their consent. This is especially a concern when those in authority are also those who are conducting, commissioning, or somehow benefiting from the research. In its extensive review of human subjects research in the military, the *Final Report* of the Advisory Committee on Human Radiation Experiments recommended that officers be specifically excluded from recruitment sessions and that an ombudsman be present to ensure that the voluntariness of participation is adequately stressed. Likewise, children can be questioned separately from their parents and confidentially. The task for the researcher is to devise a consent procedure that will adequately insulate the C-S from the hierarchical system to which he or she is subject.

### **Deferential Vulnerability**

While juridic subordination directs our attention to objective features of the formal hierarchical context within

which the C-S functions, deferential patterns are, instead, subjective responses to certain others. To be sure, the two are often present together. With respect to military officers, enlistees are generally both deferential and juridically subordinated. But when, in the presence of colleagues, friends, loved ones, and so on, one is exhorted to stand up on behalf of a popular charitable project, one may care deeply about the opinion of those significant others even though they do not, like officers, occupy formal positions of authority.

A researcher needs to understand these powerful social and cultural pressures and devise consent procedures that take them into account. There are peoples, for example, who commonly display a ready agreeableness on the surface that may mask an inner reticence. There are children who are uncomfortable taking issue with adults and third-world women who may find it hard to turn down requests from men, especially if they are respected doctors in white coats. Also included here is the Stockholm syndrome usually thought of in connection with the behavior of hostages, but also perhaps present in some heavily institutionalized subjects. The question the researcher must ask is, "Is the C-S given to patterns of deferential behavior that may mask an underlying unwillingness to participate?" The distinctive vulnerability of these subjects consists in their readiness to accede to the perceived desires of certain others notwithstanding an inner reticence to do so. Those involved in subject accrual need to be selected with care, perhaps with the advice of local informants or consultants in psychology and anthropology. The conversational setting may require attention. The challenge is to devise a process that eliminates as much as possible the social pressures that a C-S may feel even if, in reality, they are not being imposed.

### **Medical Vulnerability**

As defined here, a medically vulnerable C-S has a serious health-related condition for which there are no satisfactory remedies. Metastatic cancers can fall into this category, as can severe spinal cord injuries, Parkinson's disease, multiple sclerosis, Alzheimer's disease, end-stage AIDS, and so on. Also included are illnesses for which there are treatments that are not suitable for particular patients. For example, because it requires the use of blood products, rescue therapy for cancer, though effective, would not be a satisfactory treatment for most Jehovah's Witnesses. The question for the researcher is, "Has the C-S been selected, in part, because he or she has a serious health-related condition for which there are no satisfactory remedies?" A medically vulnerable research subject knows he or she has been chosen, in part, because of such an illness. What makes these patients vulnerable is their medically exigent state. Having run out of options, they will be willing—even eager—to undergo risks that would ordinarily be foolish. As Christiaan Barnard observed, it makes sense to leap into a crocodile-infested river to escape from a lion, but not if there is no lion.<sup>10</sup> There is an unfortunate tendency to see these patients as coerced. A gunman says, "Your money or your life." In handing over your wallet, it is important to observe that title to it does not thereby pass to the mugger. While he now has it in his possession, the wallet is still not his even though you gave it to him. Analogously, it is assumed that the infirmities of medically exigent patients strong-arm them into submission, thereby giving rise to the broadly held view that consent extorted under such duress cannot effect permissibility. This view is seriously misconceived. For facing a potentially fatal infection, I can properly consent to antibiotic treatment even though it is an equally forced choice. And having been cured, I cannot then avoid the obligation to pay my doctor's bill on the grounds that the imminent threat of death made me consent to the treatment. The deal with the doctor certainly was "your money or your life," but plainly I am obligated to pay anyway. But now observe that if my physician were to exact an exorbitant price for the antibiotic, I might properly claim that he took unfair advantage of my precarious circumstance. He exploited me. These examples help to reveal that the problem with such transactions does not reside in the agent's diminished range of choice. So instead of obsessing about "voluntariness," the presence of medical exigency should direct the researcher and the IRB to assess the fairness of the arrangement with the C-S. Is the deal exploitative? More precisely, given the interests and aspirations of both parties (and the poor bargaining position of one), is there a fair division of the benefits and burdens of cooperation?

The classic problem with research on medically vulnerable patients is an apparently ineliminable therapeutic misconception affecting the majority of these subjects.<sup>11</sup> The patients know there are no satisfactory standard treatments and that, based on preclinical research, scientists are testing a drug that might be safe and effective. Despite warnings to the contrary, these subjects characteristically enter trials on the chance they will benefit

from access to a drug that works. But Phase I clinical trials are not supposed to be about efficacy: They are designed to assess pharmacokinetics and safety. The research subject is vulnerable—so the story goes—because he or she is driven by a false but persistent hope for a cure and, accordingly, is likely to enter the study out of an unreasonable expectation of success.

Consider, for example, a fairly common protocol used in Phase I cancer research. Successive cohorts receive escalated dosages, reaching a theoretically therapeutic range toward the end of the trial. There might be six cohorts with three patients each. The first begins to receive dosage D1 at time T1. After an interval, at time T2, a second cohort begins receiving higher dosage D2. Patients at D1 continue to receive the drug only until their tumors progress by some predetermined degree or serious adverse reactions to the drug begin to appear. Assuming no adverse reactions stop the study, successive cohorts continue to enter at increasing dosages until, at the end of the last interval, six cohorts have received escalated doses for fixed intervals and the study ends. Although evidence of therapeutic efficacy might appear, researchers are not supposed to be looking for it. If it seems the drug can be taken at theoretically therapeutic levels without serious adverse reactions, Phase II and Phase III trials will be run to establish efficacy and optimum dosage.

Now even if the drug is, in reality, both safe and effective, it is often unlikely that a medically exigent research subject can benefit from it. First, patients in the early cohorts may receive theoretically subtherapeutic dosages. While researchers might have some reason to believe the drug is safe and effective, they do not have any expectation that efficacy can appear at those low dosages. When tumors progress, as they are expected to, those patients are removed from the study. Accordingly, these subjects run the risk of an adverse reaction without a compensating theoretical chance of benefit. And second, even if efficacy were to appear, the trial can end, leaving in the lurch patients who may be improving. There is commonly no guarantee that the drug will be made available, beyond the end of the trial, to research subjects who might be benefiting from it. Given the improbability of benefit, consent procedures in Phase I trials often emphasize that there can be no promise of improvement. (Importantly, promises of improvement are rare in medicine generally.) But notwithstanding the caveats in the consent forms, it is evident that hope for remission or cure motivates the majority of Phase I subjects. One solution might be to beef up the disclaimers in Phase I consents. C-Ss could be solemnly warned that, even if the drug works, they might not get a dose large enough to do any good and, even if they did get such a dose and, accordingly, began to recover, they still would not be allowed to continue on it after the trial ended.

But these admonitions are unnecessary. Instead I suggest that clinical trials on medically vulnerable patients, in addition to being structured as scientifically sound, also be designed to maximize the likelihood of subject benefit. Patients should be assured they *will* have a chance of benefiting from participation *if* it turns out that the drug is safe and effective.

Consider, for example, a redesign of the Phase I trial described above. Once again, the first cohort enters at time T1 at dosage D1. As before, a second cohort enters at T2 and D2. Assuming that, at T3, no serious adverse reactions have appeared for the subjects at D2, a third cohort then enters at D3 *and those whose tumors have progressed in the first cohort may have their dosages raised to D2*. In general, any subject whose tumor has progressed may advance to the next higher dosage, but only if and when no serious adverse reactions have occurred with the subjects who have just completed an interval at that dosage. Under this design, subjects enter onto the study with the guarantee that there are only five ways in which they will come off it. Either (#1) they choose to leave the study, or (#2) they seriously fail to comply with the protocol, or (#3) significant adverse reactions are seen in response to the drug, or (#4) they die, or (#5) they are cured. While C-Ss should be assured that #5 is unlikely, the study design takes seriously the medically exigent patient's overriding interest in maximizing the possibility of therapeutic benefit.

But it also turns out that this revised design improves the scientific output of the study. In the first place, while it generates the same dose-related toxicity data that the initial version did, the revised study is better at revealing cumulative toxicity. This is because patients can stay on the revised protocol longer, well after their tumors progress. And because it can become evident sooner that the intervention is unsafe, the research effort

can be halted sooner, reducing wasted research funds. Second, there would be fewer dropouts under this arrangement, and participation might be more attractive. Third, in the event that tumor growth is slowed, stopped, or reversed, the revised Phase I trial can evolve gradually into an early Phase II trial, accelerating the demonstration of efficacy. Finally, it should be added that this design may be especially appropriate for biologic approaches to cancer: angiogenesis inhibitors, for example, as opposed to cytotoxic agents. Adverse reactions are less of a concern with these therapies, and it is not as critical to determine the maximum tolerated dose. The redesigned study effects a fairer distribution of the benefits and burdens of cooperation. It is a less exploitative arrangement. Under this maximum therapeutic benefit standard, the primary concern would still be the scientific validity of the research design. But, having satisfied that requirement, the patient's powerful interest in improvement would have to appear prominently on the researcher's radar screen. It must be explicitly acknowledged that medical exigency can justify a departure from the norm separating research and therapy. The conjoining of these two different purposes is justified when 1) illness is severe and 2) no safe, effective, and otherwise satisfactory treatments are available. It becomes reasonable to swim with the crocodiles. While there would still be ineliminable risks associated with receiving an unproven treatment—and no basis for any promise of improvement—the researcher could truthfully say that the study is designed to give each subject the maximum likelihood of benefit *if the drug turns out to be safe and effective*. To be sure, that is still far less than these patients want, but it is also far more than most of them now receive.

### **Allocational Vulnerability**

If the internal benefit of research is a safe and effective therapy, the external benefits are the various other compensations research subjects receive. The patient in a state of medical exigency may be desperate for the internal benefit of research: a cure with a return to health. But those in a state of allocational disadvantage are seriously lacking in other socially distributed goods: money, housing, medical care, childcare, burial benefits, opportunities to benefit the community, and so on. The question for the investigator is, "Is the C-S seriously lacking in important social goods that will be provided as a consequence of his or her participation in research?" (On occasion, it may also be pertinent to ask whether the C-S is seriously burdened with social evils that will be relieved as a consequence of participation. This issue is especially pertinent for research on prisoners.)

Now, broadly, if Job-Seeker is destitute and hungry, and Business-Owner offers him a good job at a decent wage, and Job-Seeker accepts (notwithstanding that it is the only acceptable option), we wouldn't concern ourselves with the voluntariness of the acceptance so long as the terms of the arrangement were fair. But if, on the other hand, Business-Owner is offering sub-subsistence compensation, and the work is dangerous, and there are no workers' compensation benefits for the injuries sustained, we are likely to invalidate the agreement. We will do this, not because Job-Seeker had no other choice, but because the bargain was unconscionably exploitative. As with medical exigency, the vulnerability is to be found in Job-Seeker's precarious position: economic in this instance. But this allocational disadvantage should direct our attention to the substance of the bargain: Is it fair to the party in the weaker position? The minimum wage, job safety regulations, and workers' compensation benefits are all broadly supported means of reducing such exploitation.

In biomedical research, the vulnerabilities associated with allocational disadvantage can arise in many ways. The researcher needs to ask whether the deprivation has led to acceptance of an exploitative offer. For persons lacking access to health care, participation in a clinical trial may provide essential services they have gone without. Prisoners, having lost their liberty, reside in an environment that is carefully designed to shut off opportunities: They may have no other chance to be of service to their communities. Children, whose discretionary economic resources can be scant, may be eager to endure sacrifice for the sake of a toy store gift certificate. Soldiers might seek out exemption from combat duty. Psychology students may lack the credits required for a degree. While allocations are often the result of impersonal socio-economic forces, the basis for ethical concern is compounded when someone with juridic authority over the C-S is distributing the goods in question. Prisons and the military, for example, may function in this way.

While it is easy to identify the allocational disadvantages in some cases, it is often harder to discern the difference between just and unjust compensation packages. Of the six types of vulnerability, allocational



disadvantage is probably the most problematic. We are often inclined to honor the view that, if a bargain is satisfactory to both parties, third parties should not interfere. But participation as a subject in medical research can impose risks and burdens that properly attract community attention. While we do not want to see people treated unfairly, we are not very confident applying the concept of the just price.

At a minimum, I suggest we consider the standards we routinely apply to other comparable remunerative activities. Although the point has been urged before, it is hard to grasp why research subjects should not normally be entitled to medical treatment for the injuries they suffer and why they should be asked to subsidize the research enterprise in that unusually burdensome way. Surely if we extended broad community standards into this aspect of research, we would begin by securing a right to some version of workers' compensation.

### **Infrastructural Vulnerability**

Although IRBs, researchers, and subjects often take them for granted, there are many protections and resources that contribute importantly to the safety of the research subject. When a consent form asks subjects to call a listed telephone number if they have a question or complaint, those phrases presuppose access to a telephone system. When a protocol requires the long-term use of frozen biological agents, that provision presupposes a reliable supply of electricity. When an investigational drug regimen has to be skillfully administered, the researchers may be assuming the availability of skilled health care professionals and a responsible independent local review mechanism. At the structural level, essential political, legal, regulative, institutional, and economic resources may be missing, leaving the subject open to heightened risk. The question for the researcher is, "Does the political, organizational, economic, and social context of the research setting possess the integrity and resources needed to manage the study?"

Although egregious failings are likely to be more common in international research—particularly in undeveloped areas—it should not be assumed that U.S. citizens will always enjoy the protections most of us take for granted. Increasingly we hear of ethically flawed research at well-known universities where investigators are plainly confused about the ethical dimensions of their work and the review and monitoring committees are untrained, underfunded, and understaffed. Where procedures permit the participation of IRB members with conflicts of interest, the disinterested review of protocols may be an illusion.

Clearly the possibility of infrastructural vulnerability calls for attention to the contexts within which the research will be done. To some extent, national or international certifying bodies may be able to carry out the fieldwork for such inquiry: It may not be feasible for American research institutions to assess the resources in communities on the other side of the planet. Perhaps single or multiple project assurances can be secured from international partners: Pertinent inquiries could be directed to them.

### **Recommendations and Concluding Reflections**

I have reconnoitered the terrain of vulnerability in research subjects, offering what we believe to be a more productive, a more nuanced account of the topic. I have tried to provide criteria for six discrete types, describing how each can impair the connection between consent and permissibility, I have alluded to some of the issues researchers might address in undertaking to accommodate the special needs of the vulnerable.

In the light of that discussion, the primary recommendation of this paper is that the traditional focus on discrete vulnerable subpopulations must now give way to something like the analytical framework proposed above. It is not now possible to develop subparts for every allegedly vulnerable group, and, even if it were, the absence of clear criteria for admission can only result in the politicization of our mechanisms for the protection of human subjects. What is needed is clear thinking about the species of human precariousness and the ethical response each calls for in the context of clinical research. The development of subparts could follow, but only if they are informed by a defensible analytical framework.

In the course of discussion, a number of more specific recommendations have been made. While more

needs to be said about all of these, two suggestions are worth underlining. First, clinical trials should take far more seriously the needs of medically vulnerable research subjects. While good scientific design is a *sine qua non*, researchers should also be required to consider how they might provide maximum therapeutic benefit for patients who have run out of options. And, second, we need to consider the fair entitlements of research subjects who are disadvantaged in economic and other ways. It is a worry that we may be tolerating unfair arrangements in the context of clinical research that we would not find acceptable elsewhere.

Although the point has not been developed, it should be clear that members of a population may exhibit several types of vulnerability. Indeed research subjects can illustrate all six. For example, an eight-year-old girl in a third-world country could display cognitive limitations, could be under the authority of her parents or village elders, could be exceedingly deferential to any adults who are respected by her parents, could suffer from a serious medical condition for which there are no available treatments, could be lacking in general medical attention that would be provided in the course of the study, and could live in an environment in which resources critical to the success of the study were not reliably available. Instead of developing a discrete subpart for children (and assuming that when those regulations were satisfied, research on a child could then proceed), the analytic focus recommended here would highlight six problematics, each requiring further inquiry and, potentially, the implementation of compensating mechanisms.

While it still might make sense to develop standards and regulations for recurring subpopulations, these could no doubt be improved by concerted attention to something like the taxonomy of vulnerabilities that is set out here. It is possible to envision the eventual development of a master matrix, the columns of which would be subpopulations and the rows of which would be the pertinent vulnerabilities, each cell detailing the compensating measures that might address them. Initially, such a resource could be developed from a review of ideas already recorded in approved protocols and on internet-based bulletin boards, such as MCWIRB. It would take funds and a concerted organizational effort to bring forth such a tool, crafting it as a living consensus document, continually improved by broadly submitted commentary and authoritative updates by well-respected advisory boards. And yet the availability of web-based and hardcopy versions of the matrix could be the most effective means of helping researchers and IRB members to measure up to the highest ethical standards in their work. Having served on an IRB, I can attest to the potential usefulness of such a resource.

Finally, it seems that the sensitive understanding of vulnerability—the many precariousnesses that afflict the human condition—exposes a certain universality in these themes even while grounding a broader case for kindness and sensitivity. None of us is without some cognitive limitation. Everyone is subject to juridic authority, not all of which is wisely benevolent. Socialization itself entails patterns of deference. All of us face an eventual and too real prospect of medical exigency. And no one is immune from extreme need and the harms that can flow from deficits in the systems we count on to provide us with essential services and protections. Nor are researchers the only ones who need to learn how to engage the vulnerable with sensitivity and honor. The topic surely has an importance extending beyond the boundaries of research ethics.

## Notes

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