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Evaluating Biomedical Enhancement Research: Assessing Risk & Benefit and Obtaining Informed Consent

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Abstract

There are two primary human subject protections: assessing and comparing the risks and potential benefits of proposed research, and obtaining potential subjects' informed consent. While there has been extensive discussion in the literature on these two aspects, no attention has been paid to whether the processes should be different when the objective of an experimental biomedical intervention is to improve individual performance or capacity ("enhancement research") rather than to prevent, cure, or mitigate disease ("health-oriented research"). This essay examines how both assessment of risks and benefits, and obtaining informed consent in an enhancement experiment might differ from the approaches used in health-oriented investigations, and considers appropriate protections for subjects in enhancement research.

There are two critical steps in determining whether a medical experiment involving human subjects can be conducted in an ethical manner: assessing risks and potential benefits and obtaining potential subjects' informed consent. Although there is an extensive literature on both of these aspects, virtually nothing has been written about human experimentation for which the objective is not to prevent, cure, or mitigate a disease or condition, but to enhance human capabilities. One exception is a 2004 article by Dresser on preimplantation genetic modification—one of the most controversial enhancement technologies—in which she states: "Under existing research ethics principles, it would be unethical for investigators to perform modifications exposing embryos expected to develop into healthy children to significant risk in exchange for a possible physical or mental enhancement."¹ But Dresser does not explain why such an experiment would be unethical under existing principles, and her conclusion is not self-evident.

Providing guidance on how to assess risks and benefits and obtain informed consent in enhancement research is important because of the growing interest in biomedical techniques for improving human traits and capabilities, including cosmetic surgery, performance-enhancing substances in sports, interventions to retard or reverse aging, tests for non-disease genetic variations, drugs to improve cognition, mood, and sexual performance, and biomedical techniques for making soldiers better war fighters. Although the Food and Drug Administration (FDA) has approved medical indications for many of these drugs and devices, few of them have been subjected to formal clinical investigation and approved for enhancement uses, and physicians who provide access to them for enhancement purposes do so on an "off-label" basis. But increasing demand for enhancements that are safe and effective, coupled with FDA impediments on marketing products for off-label uses, suggests that manufacturers may become more interested in sponsoring full-scale clinical trials in order to obtain licensing approval for enhancement indications. The Defense Department and the armed services already engage in extensive enhancement research.² Physicians may

pressure the NIH to fund enhancement studies in order to generate information that they can use in advising their patients. Sports organizations may need to conduct human experiments to validate their anti-doping testing methodology.³ An understanding of how to protect subjects in enhancement research therefore seems essential. This paper attempts to address this need by considering how analysis might differ between health-oriented and enhancement studies, and how to protect competent adult human subjects in enhancement research. Part A defines enhancement research. Part B explores assessments of risks and benefits in both health-oriented and enhancement research. Part C analyzes the informed consent requirements in the federal research regulations and applies them to enhancement research. Part D concludes.

A. What is Enhancement Research?

The distinction between enhancement and health-oriented research is not a bright line. A working definition of biomedical enhancement is that it is an intervention that employs medical and biological technology to improve performance, appearance, or capability, and thus, according to Oxford professor Julian Savulescu, “increases the chances of leading a good life.”⁴ Often, an enhancement will place a person beyond the population norm, but this need not always be the case. If an individual started out within the normal range, for example, an improvement would be an enhancement even if it left the individual within the normal range. (Indeed, persons with below-normal ability to begin with might be said to have been enhanced not only if they achieved a better-than-normal ability, but if they ended up normal but significantly better than average.)

The concept of “normality,” of course, is itself elusive. In some cases, it refers to the frequency with which a trait or capability occurs within a population. In other circumstances, it may have no relationship to the distribution of a trait. (Normal eyesight is deemed to be 20/20, for example, but only about 35 percent of adults have 20/20 vision without some form of correction.⁵) Standards of normality may vary from place to place and time to time, and they can be expected to change as the use of enhancements increases.

An enhancement does not aim to prevent, treat, or mitigate the effects of a disease or disorder. Thus, immunization, which makes people’s immune systems better than normal, is not an enhancement. The concepts of disease and disorder are also hard to pin down, however. Witness the controversy over whether aging is or is not a disease.⁶ Body shapes that were associated with health a hundred years ago are now considered obese. Moreover, there is a tendency to regard more and more health states as diseases and more and more interventions as treatments.

In the end, then, the distinction between health-oriented and enhancement interventions will not always be clear, and invariably there will be borderline cases. The same will be true when trying to distinguish health-oriented from enhancement research. Indeed, health-oriented clinical studies that employ normal subjects as controls might enable the investigators to detect enhancement as well as health-oriented effects. For example, Apud, et al. studied the drug Tolcapone, an inhibitor of catecholamine-*O*-methyltransferase, to ascertain if it improved cognitive function in schizophrenics. But in the process, they identified a cognition-enhancing effect in their normal controls.⁷ Investigators even might intentionally embed an enhancement study within a study of treatment for a medical condition, in the hope that an IRB would be more likely to approve the protocol than if it looked like an outright enhancement study.

This paper addresses a particular type of enhancement research, in which the experimental intervention is biomedical in nature. There are many other ways of enhancing a person’s capabilities that might be the subject of research with human subjects, including education,

experience, and the use of mechanical aids. As with the distinction between enhancement and therapy, it may be difficult to draw the line between biomedical and other types of enhancements. For example, how should we classify prostheses, implanted computer chips, and nanotechnology? This paper focuses on enhancement experimentation involving drugs, biologics, and medical devices, since that more closely resembles health-oriented clinical research than psycho-social research, and therefore is more likely to invite comparison with the ethical rules that currently govern clinical experimentation.

B. Assessing Risks and Benefits

1. Health-Oriented Research

The basic ethical principles that govern human subjects research are enshrined in federal regulations. Investigators, institutional review boards, government sponsors, and government regulators must satisfy themselves that the benefits are maximized and the risks minimized, and that the risks are reasonable in relation to the anticipated benefits, including benefits to subjects and the importance of the knowledge to be gained.⁸ If these entities are satisfied with the results of their assessment, then and only then may investigators proceed to seek informed consent from potential subjects.

Emanuel, Wendler, and Grady describe the assessment of risks and benefits as comprising three basic steps: First, the risks are identified. Second, potential benefits to subjects are delineated and “enhanced,” that is, measures are identified that could increase the potential benefits for subjects. Third, the risks and benefits are compared.⁹ The authors add an additional step in the event that the study presents no prospect of direct benefit to the subjects: determining whether the potential societal benefits in terms of knowledge outweigh the risks to individual participants.

Weijer and Miller note that studies often involve “a mixture of interventions administered with differing purposes.”¹⁰ In response, they describe a method they call “component analysis” to more clearly distinguish between the therapeutic (that is, presenting the prospect of direct benefit to subjects) and non-therapeutic (presenting no prospect of direct benefit to subjects) aspects of a study. Component analysis involves two separate sets of norms: in the case of non-therapeutic procedures, reviewers must ascertain that the risks “are minimized consistent with sound scientific design,” and that they are “reasonable in light of the knowledge to be gained.” Therapeutic procedures, on the other hand, must meet the standard of “clinical equipoise,” must be “consistent with competent care,” and must entail risks that are “reasonable in relation to potential benefits to subjects.”

Clinical equipoise means that there is genuine uncertainty within the expert medical community about relative therapeutic merits of the experimental and control treatments that will be evaluated in the trial.¹¹ According to this standard, a study is unethical if subjects will be denied access to a therapeutic intervention that a consensus of medical experts believes is appropriate given the subjects’ condition. Not all ethicists agree that clinical equipoise is the appropriate principle. Some argue that it obfuscates the distinction between therapy and research, and that research often requires investigators to deviate from the standard of care, for example, by employing randomization and placebo controls.¹² Miller and Wendler recommend a “net risks test” instead of component analysis and clinical equipoise.¹³ Morreim goes so far as to contend that, unlike treating physicians, researchers are not “fiduciaries” for subjects, and therefore need not place the welfare of subjects in all respects above the success of the research endeavor.¹⁴ Other ethicists, applying what they call the “uncertainty test,” maintain that reviewers must eschew reliance on the collective judgment of the medical community and instead make their own determination about what is

best for the subjects; in their opinion, a study is ethical only if the reviewer personally is uncertain about what constitutes the standard of care.¹⁵

The role of reviewers in assessing the social implications of research also is unclear. On the one hand, funding agencies like the NIH consider whether studies they are asked to finance could produce findings that were not in the public interest. In connection with research on gene transfer technology, for example, the NIH requires investigators to describe “any potential benefits and hazards of the proposed gene transfer to persons other than the human subjects receiving the experimental treatment,”¹⁶ and what steps they will take “to ensure that accurate and appropriate information is made available to the public with respect to such public concerns as may arise from the proposed study.”¹⁷ Moreover, the Common Rule instructs IRBs to “take into account the purposes of the research ...” in assuring that the selection of subjects is equitable (45 CFR §46.111(a)(3)), and gives IRBs the responsibility of assuring that “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result . . .” (45 CFR §46.111(a)(2)). Thus, IRBs should not approve a protocol that imposes significant risks on subjects but that would not produce any direct benefit for them and would yield scientific knowledge only of little importance. This leads many research ethicists to conclude that IRBs are empowered to consider the potential social consequences of a proposed investigation. Emanuel and his colleagues state, for example, that IRBs must determine “when potential social benefits outweigh risks to individual subjects.”⁵ One experiment indeed found that IRB members approved hypothetical “socially-sensitive” protocols (proposing to document racial or gender biases in corporate hiring) only 40–50 percent of the time, compared to 90 percent for nonsensitive proposals (examining hiring practices based on height or weight).¹⁸ But the regulations go on to caution that “[t]he IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.” (45 CFR §46.111(a)(2)). According to one of the key staffers of the commission that produced the Belmont Report, this restriction stemmed from concerns that IRBs might block social science research, such as research on race and intelligence, on the ground that it might produce socially undesirable findings.¹⁹ The commission felt that IRBs lacked the expertise to assess the long term policy impacts of research, and that these impacts were too speculative in any event. Therefore, while IRBs clearly must consider the importance of the knowledge to be gained from a proposed trial, it is not certain that they are empowered to assess the potential harms to society that might flow from the experimental technology, at least not if these harms would affect public policy.

2. Enhancement Research

Given the difference in their objectives, it might be supposed that health-oriented and enhancement research would differ in a number of ethically significant respects. Yet they are likely to be similar in many ways. Properly designed studies would employ the same basic steps: stating a problem; formulating a testable hypothesis; using appropriate methodology to gather data; and using appropriate statistical analyses of results. Both types of experiments should be expected to minimize the risks to subjects and maximize the benefits, and in both cases, the risks should be reasonable in relation to the anticipated benefits. Moreover, an enhancement investigation is just as likely as a health-oriented investigation to combine both “therapeutic” and “non-therapeutic” aspects, insofar as these terms are interpreted to refer respectively to research that may provide a direct benefit to subjects and research that will not provide a direct benefit to subjects but instead produce generalisable scientific knowledge. Therefore it would seem appropriate to apply Weijer and Miller’s approach to assessing risk and benefit in relation to the non-direct-benefit aspects of

an enhancement study, that is, making sure that the risks are minimized and are reasonable in view of the value of the knowledge to be gained.

It might be supposed that enhancement research would rely on different methods for assessing benefit, and that enhancement investigations would be more likely to rely on qualitative, subjective measures. Upon closer consideration, however, the methodologies for assessing benefit are likely to be strikingly similar. Both health-oriented and enhancement research may employ qualitative, quantitative, objective, and/or subjective measures, and there is no reason to assume that enhancement research would rely more than health-oriented research on qualitative or subjective measures. Consider a surgical intervention such as plastic surgery of the nose that can be employed for an enhancement purpose (a rhinoplasty or “nose job”) or for the purpose of correcting a nasal malformation or injury. In either case, benefits presumably would be assessed in terms of pre-and post -surgical nasal air flow (quantitative, objective), as well as aesthetic appearance (qualitative, subjective).²⁰ Research on pharmacologic agents to enhance mood similarly would rely on the same quantitative, subjective instruments to measure benefit as research to alleviate clinical depression: quality-of-life, social interaction, and depression rating scales (although these might have to extend their range to distinguish between different degrees of positive states).²¹ Research on pharmacologic agents to improve cognition in mentally retarded and normal individuals would employ the same tests of cognitive ability. A refractive eye surgery technique (e.g., LASIK) might be tested to see if it can correct a subject’s vision to 20/20 (health-oriented), or to see if it can enhance vision to better than 20/20 (enhancement). In either case, researchers would measure the same benefit, improvement in vision, using the same techniques. Experiments to determine if gene insertion facilitated muscle growth would assess similar risks and benefits regardless of whether the subjects were patients suffering from muscle-wasting disease or athletes seeking to improve performance. Restorative medical interventions (e.g., reconstructive surgery) would refer back to pre-traumatic appearance as the baseline state for assessing benefit; similarly, one measure of benefit in enhancement surgery is likely to be the difference between post-intervention appearance or function and the pre-intervention baseline state.²²

Both enhancement and health-oriented research can create medical and non-medical risks. Using Levine’s classification of research risks, subjects in both types of experiments may suffer bodily harm (physical risk), negative impacts on their mental states (psychological risk), social stigma (social risk), and financial costs (economic risk).²³ LASIK surgery researchers, for example, would monitor the same risks (flap complications, dry eye, infection, etc.) whether the goal was correction or enhancement. Experiments to determine if gene insertion facilitated muscle growth would assess similar risks, such as the safety of the viral gene vector, regardless of whether the subjects were patients suffering from a muscle-wasting disease or athletes seeking to improve performance. Subjects in both types of investigations may face non-medical risks in the form of threats to privacy and confidentiality.

A fundamental tenet of research ethics is that the greater the risks of a clinical experiment, the greater the potential benefit that is required. The degree of potential benefit is a product of the nature of the benefit as well as its amount. The more important or valuable the potential benefit, the greater the risks that researchers ethically can impose on subjects. As the Declaration of Helsinki proclaims: “Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject.”²⁴ The Nuremberg Code agrees that “[t]he degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.”²⁵ It might be wondered, therefore, whether the benefit from an enhancement was inherently less valuable than a health-oriented intervention, so that it

would be ethical to conduct an enhancement study that created the same risk for subjects as a health-oriented study only if the potential benefits were expected to be greater, perhaps substantially.

On the one hand, it might seem obvious that medical benefits are inherently more valuable than enhancement benefits. Health is often described as a “special,” “basic,” or “primary” good,²⁶ without which it is impossible to attain “normal species functioning”²⁷ or to enjoy a reasonable range of opportunities.²⁸ It would be highly unlikely, for example, that the National Institutes of Health would invest a significant portion of scarce research funds in enhancement rather than health-oriented research. If enhancements have less inherent value than medical interventions, then it might seem unethical to expose enhancement subjects to the same amount of risk as subjects in health-oriented experiments. A study of a new plastic surgery technique with more than a minimum of risk might be justified in subjects who required nasal reconstruction, but not in subjects who sought nose jobs. Moreover, some enhancement technologies, such as those involving genetic factors in illness, are new and their risks poorly understood. As one commentator states, “[i]f the safety of a treatment is relatively unknown ... a larger potential benefit might reasonably be required.”²⁹ Finally, commentators argue that, since subjects in enhancement studies are healthy, whereas subjects in medical experiments are ill to begin with, enhancement subjects have more to lose and therefore researchers must offer them greater benefits for a given amount of risk. Nicholas Agar states, for example, that “[t]he cost/benefit analysis is different for enhancement. While those who are experimenting with treatments for serious diseases may only succeed in substituting one kind of misery for another, those experimenting on human enhancement are likely to substitute a miserable life for a happy one.”³⁰

But the value of a benefit clearly depends on the nature of the benefit. It is reasonable to expect that some health-oriented benefits would be regarded as more valuable than some enhancement benefits. Most people probably would agree that an experiment to test a potentially life-saving drug or medical device posed an opportunity for greater benefit than an experiment to test a new non-prescription contact lens like Bausch and Lomb’s MAXSIGHT™, which reduces glare for athletes and makes them appear more ferocious. On the other hand, some enhancement benefits may be perceived as more valuable than medical benefits. An enhancement that potentially increased cognitive function substantially, for example, might be deemed more valuable than a substance to treat a minor skin irritation. In short, in both health-oriented and enhancement research, the potential benefit necessary to justify a set of risks will depend on the specifics of the study in question.

Finally, the question arises whether enhancement research should rely on the same division of responsibility between experts and subjects for assessing risks and benefits as other types of biomedical research. Under the rules currently governing human subjects research, investigators may approach potential subjects to seek their informed consent to participate only after experts—in the form of the investigators themselves, institutional review boards, government sponsors, and government regulators—have determined that the risks of proposed investigations have been minimized and are reasonable in light of the potential benefits. The Belmont Report grounds this sequence in beneficence: “Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. ... Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.”³¹

Yet one neurologist observes that, “[a]s neurologists, we may have special understanding of the potential benefits and risks of quality of life therapies in so far as they work through the

nervous system. But we have no special insight into the pursuit of happiness.”³² The President’s Council on Bioethics, no friend of biomedical enhancement, also is skeptical that medical expertise carries over to assessing the benefits of enhancement:

[T]here are difficulties when medical practice moves beyond therapy. Where the goal is restoring health, the doctor’s discretion is guided by an agreed-upon and recognizable target. But a physician prescribing for goals beyond therapy is in uncharted waters. Although fully armed with the means, he has no special expertise regarding the end—neither what it is nor whether it is desirable.³³

This observation would seem to suggest that competent adult subjects should be allowed to decide for themselves if the potential benefits of participating in enhancement research outweighed the risks, rather than being required to defer initially to the judgment of medical experts.

It would be perilous to the welfare of enhancement subjects, however, to leave them without the protection of prior expert risk/benefit assessment. In reviewing research protocols, experts can help protect subjects from careless, unscrupulous, or incompetent researchers who do not properly design investigations to enable them to yield valid and reproducible results; misrepresent the potential benefits; deemphasize risks; fail to disclose information necessary for informed consent; devalue subjects’ welfare; or present a conflict of interest that poses a risk of harm to subjects. Experts also have a critical role to play in protecting vulnerable subjects who have a diminished capacity for assessing risks and benefits and for giving truly informed consent. Finally, the requirement that experts consider the risks of an enhancement experiment to be reasonable in light of the potential benefits may be essential in ensuring that individuals do not agree to serve as subjects under a therapeutic misconception or because they are under undue pressure to participate. We will return to this point later.

So far, the job of assessing risks and potential benefits in enhancement research does not seem to differ significantly from the assessment approach called for in health-oriented research. But there are several respects in which the approach to assessing risks and benefits in the two types of studies may not be the same. It is not clear, for example, if component analysis, which as noted earlier incorporates a requirement of clinical equipoise, would be appropriate in the context of enhancement research. Component analysis rests on a distinction between therapeutic and non-therapeutic research, and by “therapeutic” it seems to have in mind research that presents the prospect of direct health benefits to patients serving as subjects. Since the subjects in enhancement research ordinarily would not be patients in need of treatment, it may not be appropriate to consider direct benefits that they might receive as “therapeutic,” and therefore to require that the study design meet the standard of clinical equipoise. Moreover, this standard would seem to require uncertainty within the relevant expert community about the relative enhancement merits of the experimental and control interventions that were being compared in the trial. If a study proposed to evaluate the cognition-enhancing effects of a drug against a placebo, for example, there would have to be uncertainty over whether there were any effective methods for enhancing cognitive ability. If the community of experts regarded, say, tutoring or mental exercises as effective means of enhancing cognition, the clinical equipoise test would seem to allow the study to proceed only if the experts were uncertain about the relative merits of these techniques compared with the experimental drug, and then only if patients were randomized into groups receiving either these techniques or the experimental drug, and not a placebo. Yet it does not seem necessarily unethical to allow normal subjects to enroll in an enhancement experiment without being given access to other methods of enhancing themselves, even when the other methods are well-recognized. It would seem appropriate to hold physicians acting as researchers to a standard of medical competency in the manner in

which they administered the enhancement intervention to subjects, conducted medical testing related to the study, and monitored adverse effects, but it is not clear that they would owe subjects the same duty of care when the experimental intervention is an enhancement as when the subjects were patients in need of health care. Indeed, some ethicists may question whether enhancement is an appropriate field of practice for physicians at all.

Another problem that could arise in applying the clinical equipoise standard to enhancement trials is identifying the appropriate expert community. In a study of a drug to enhance cognition, would the appropriate community be physicians, psychologists, educators? What if these communities did not agree on what other methods might be effective for enhancing cognition? If the experiment involved a biomedical intervention to enhance athletic performance, would the appropriate community of experts be sports physicians? Trainers? Athletes? In a study of an intervention to enhance sexual performance, would the experts be urologists? Porn stars? Identifying the appropriate expert community also could be complicated in the case of health-oriented trials, but it may be more difficult in enhancement research because of the greater diversity of fields of relevant expertise.

An additional respect in which the assessment of risks and benefits in enhancement research might seem to be different than in health-oriented research involves social impacts. Enhancement research raises social and ethical objections, such as that enhancement is unnatural³⁴; takes the place of earned achievement, and therefore yields undeserved social rewards³⁵; interferes with authenticity³⁶; or exacerbates socio-economic inequalities.³⁷ This might be thought to call for greater skepticism in assessing potential enhancement benefits and in offsetting benefits against risks.

Yet some of these same objections also might be asserted against research leading to effective therapies and preventive measures. Insofar as illnesses are naturally caused, treatments and preventions interfere with the natural state.³⁸ Expensive, new treatments may be unaffordable for many, and health disparities based on race and income are well-documented.³⁹ Furthermore, the classic expression of concern about authenticity was not made in regard to enhancement, but in reference to the therapeutic use of anti-depressants.⁴⁰

The only objection raised by enhancements that does not seem to apply to medical interventions is that enhancements might yield undeserved social rewards. This concern is too complex to be addressed fully here, but suffice it to say that many social rewards are the product of luck and natural talent, neither of which are deserved.⁴¹ Furthermore, enhancements may have significant positive social impacts. It is true that some enhancements, such as designer steroids that evade detection in sports, not only might provide no benefit, but might produce a net social loss. But other enhancements might be highly beneficial. Yesavage and colleagues tested the Alzheimer's drug donepezil (AriceptTM) in airline pilots, and found that it improved the subjects' ability to respond to simulated, in-flight emergencies.⁴² While steroids produce little social benefit in sports, they may be highly beneficial in rescue work. There remains the controversial issue of the extent to which potential societal benefits can outweigh risks to experimental subjects, but there is no *a priori* reason to assume that the answer would be different for enhancement as opposed to medical research.

C. Informed Consent

Assuming that enhancement research clears the initial assessment of risks and benefits, a second set of protections governs the informed consent process. Informed consent is one of the basic ethical protections for research involving human participants.⁴³ It is designed both to increase individual welfare and to facilitate autonomy.⁴⁴ It increases welfare because participants are best situated to weigh personal factors along with medical information to

make the best choice of whether to take part in the research. It increases autonomy because informing participants and asking them to make a choice allows them to exercise control over their bodies and their lives. The doctrine of informed consent was shaped to achieve these dual goals.

Research informed consent, like treatment informed consent, requires disclosure of certain information and an opportunity for the individual to decide whether to participate in either research or treatment. The elements of informed consent are laid out in moderate detail in a series of Health and Human Services (HHS)⁴⁵ and Food and Drug Administration (FDA)⁴⁶ regulations, which together form what is known as the “Common Rule.” According to the Common Rule, participants must be given a written⁴⁷ document including, among other things:

1. A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts
3. A description of any benefit to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternatives procedures or courses of treatment, if any, that might be advantageous to the subject;⁴⁸

Additional protections around the informed consent process are required for specific populations, e.g., pregnant women, fetuses and neonates;⁴⁹ prisoners;⁵⁰ and children.⁵¹ Safeguards may also be required for any other population deemed “vulnerable to coercion or undue influence, such as... mentally disabled persons, or economically or educationally disadvantaged person.”⁵² The following sections address some of the issues raised by these requirements in the context of enhancement research.

1. Identifying Information for Disclosure

The first issue raised by enhancement research has to do with identifying the information that needs to be included in the consent. The weight to be given enhancement benefits in the initial risk-benefit evaluation is discussed above. From the informed consent perspective, the issue is whether an enhancement benefit counts as a benefit that should be disclosed under 45 CFR 46.116(a)(3). There is no definition of benefit in the federal guidelines and thus no reason to think that an enhancement benefit would not be included. But how should the investigator understand or describe an enhancement benefit and to what extent should the investigator’s subjective beliefs about benefit come into play?

Investigators are expected to be able to identify the purpose of a study and of any interventions used in the study and their potential benefits, in order to disclose those benefits to potential subjects. But, as pointed out previously, it may be that medical professionals can claim no special expertise with respect to enhancement interventions.⁵³ On the other hand, investigators do fairly well in disclosing altruistic and societal purposes of research in consent dialogs,⁵⁴ and perhaps they will be likewise able to appropriately frame the purpose of enhancement research. Even if the investigators can identify the non-medical purpose of the procedure, and non-medical potential risks and benefits, why should they be obligated to provide this information? If enhancement benefit is defined in subjective terms according to the preferences of the individual then why not simply state that “benefits are subjective” in the consent form? Of course, such phrasing may be difficult to pass by an Institutional Review Board (IRB) scrutinizing a consent form.⁵⁵

Likewise, how should we think about alternatives in the context of enhancements? Should investigators be required to identify other potential enhancements or other non-medical alternatives? We've stated above that alternatives may not be appropriate to consider in the risk-benefit analysis, but what about during the consent dialog? Although there is still some debate about the scope of disclosure of alternatives—investigators do not have the obligation to disclose every possible option-- for our purposes it is important to note only that the emphasis is on disclosure of medical options (i.e., those within the special expertise of the medical professionals).⁵⁶ Should this presumption change if the intervention under study is itself not within the special expertise of medical professionals?

To clarify these points about disclosure, consider a study comparing saline and silicone implants for breast augmentation. Saline implants are thought to be less risky, silicone more so.⁵⁷ But besides the benefit of lesser risk, the primary benefit difference relates to the look and feel of the implant—something the patient is best able to evaluate. Or even more difficult, how about the choice between different size implants? One can identify the potential physical health problems from extremely large breasts, but what about issues such as self-esteem, physical attractiveness, and fit of clothing?⁵⁸ Would the informed consent document and discussion need to include a description of the potential benefit of a more “natural” feeling breast? Or the “benefits” of larger breasts, regardless of the type of implant used? Would this type of study be a study involving potential direct benefit to the participants, or is it merely a study to determine relative safety with no potential for direct benefit?

Many studies have benefits other than direct therapeutic ones. There can be direct economic benefits (participants are paid), potential indirect psychosocial benefits (participants may feel altruistic and thus good about themselves), and potential indirect therapeutic benefits (participants may get better monitoring and attendant care as part of the study). Whether and how each of these should be weighed, both by the IRB in making the initial determination that the research can proceed, and by the participants in making the choice of whether or not to consent, is a matter of some debate among commentators. For example, if enhancement benefits are like direct therapeutic benefits then they can be weighed against the level of risk. But if they are more like compensation benefits then we may be less comfortable with high levels of individual risk in exchange for high potential for individual enhancement.⁵⁹ Additionally, we might be concerned about whether providing such benefits is coercive,⁶⁰ particularly for specific populations that might be disadvantaged at the outset (e.g., physical enhancements for athletes or cognitive enhancements for students). How we categorize enhancement benefits will play a role in how they should be described to potential participants as part of informed consent, and how IRBs may require they be detailed in consent forms.

The flip side of benefit identification relates to risks-- how should we think about the risks of enhancements and how should investigators explain these risks to participants? For example, should participants be told that there is a risk that they won't be happy or satisfied with the enhancement? Standards of beauty, for example, are culturally determined and often change from generation to generation. Is this an area where participants' unrealistic goals or expectations will be more problematic than in other forms of research? Or take an extreme situation -- there are suggestions that many individuals who undergo multiple cosmetic procedures have body dysmorphic image, they constantly see flaws in their bodies that others do not.⁶¹ These individuals are unlikely to be happy with the results of any procedure. Is this a risk that should be identified in the consent form? What about societal risks that use of enhancement interventions will result in people changing their views of different skills? Part of the debate about the use of steroids in baseball, for example, is a debate about whether we should view the new records as being as valid as old ones.⁶²

Although the regulations are clear that IRBs are not to consider the “possible long-range effects of applying knowledge gained in the research... as among those research risks that fall within [its] purview,”⁶³ there are no specific guidelines on how and whether to discuss non-medical risks with the individual participants.

2. Alterations of Informed Consent

45 C.F.R. 46.116(d) outlines the situation in which “[a]n IRB may approve a consent procedure which does not include, or which alters, some of all of the elements of informed consent” for adult participants.⁶⁴ In order to approve such a change the IRB must find that:

1. The research involves no more than minimal risks to the participants;
2. The waiver of alteration will not adversely affect the rights and welfare of the participants;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

Some enhancement research will fall under this minimal risk categorization and potentially fall within the exception allowing a waiver of informed consent requirements. One can imagine an example of a low risk intervention (d)(1), such as a nutritional supplement that is designed to enhance memory or recall. Suppose an investigator would like to study the supplement, but cannot inform the subject population about the exact nature of the study because providing such information will bias the results (d)(3), e.g., she would like to know if the participants recall the information better, but does not want to tell the participants about the information in question for fear it would affect recall. After the data is collected, participants will be debriefed and informed about the details of the study (d)(4), and nothing about the way in which information is kept from the participants initially will affect their rights or welfare (d)(3). This study, and alteration of informed consent, would be permissible under the federal regulations. Whether this is viewed as problematic may have to do with whether or not we accept that enhancement goals are as valid in research as treatment goals. In fact, the section in question was initially designed to allow certain types of psychological deception research to go forward.⁶⁵ So the Common Rule appears to accept that some human participants’ research will be focused on goals beyond medical treatment. Enhancement goals should likewise be acceptable, although it may be necessary to evaluate any particular goal within the context of each study, as must be done for risk-benefit assessments.

Alternatively, we might see a tendency of investigators and IRBs to “medicalize” enhancement benefits—categorizing them in terms of direct therapeutic benefits so they fit better within the traditional framework. We’ve seen hints of this in other contexts where syndromes are defined in order to justify medical intervention. Thus people who work unusual hours are sometimes diagnosed with “shift-work sleep disorder” (SWSD).⁶⁶ From one perspective the individuals suffering from SWSD do not have a sleep problem, they have a job problem (e.g., the job does not allow them normal sleep cycles). By defining the problem as a medical disorder, we view the interventions as “treatments”—to help combat excessive sleepiness, rather than enhancements—to allow people to get by on significantly less sleep than normal.

The concern that enhancement benefits will be framed in terms of direct therapeutic benefits has significant implications for research involving children. Unlike adult research where the minimal risk categorization is important for determining waivers of informed consent, for

pediatric research minimal risk categorization may determine whether research is allowed at all. Moreover, like the adult guidelines, Subpart D allows a waiver or alternation of informed consent, as well as a waiver of assent, if the requirements of 45 CFR 46.116(d) are met.⁶⁷ Waivers of informed consent in enhancement research involving children may be of more concern than waivers in enhancement research involving adults.

3. Vulnerability

Additional protections are supposed to be added to the consent process for vulnerable populations. Healthy volunteers are usually thought to be the least vulnerable participants. They are making decisions to participate based on either altruism or compensation. But are people who participate in enhancement research more like healthy volunteers or like ill participants? Everyone could use some enhancement in some area, although by definition the participant does not need the intervention to achieve, sustain or restore health. “Need” is certainly a difficult term to interpret, and there may be gradations from necessary to sustain life, to necessary to continue in the individual’s chosen profession, to necessary to compete at a professional or Olympic level, to necessary for preferred activities (e.g., knee replacement for an athletic individual). One reason for placing informed consent obligations on physicians is that they are providing (and exercising control over) services that patient-subjects “need”. The need for a service renders the individual in question vulnerable to the person who controls access to the service, and the doctrine of informed consent functions as one protection for that vulnerability.⁶⁸

Individuals seeking enhancements are not vulnerable in the same sense as those who are in need of medical treatments, but they may still be vulnerable. Consider a student who “needs” a cognitive enhancement to score well on a college or graduate school entrance exam. Former President Clinton’s National Bioethics Advisory Commission (NBAC) explored the concept of vulnerability and separated it into six categories: medical, cognitive/communicative, institutional, deferential, economic, and social.⁶⁹ NBAC stressed that “vulnerability is sensitive to context” and that protections should be tailored to the specific vulnerability in question.⁷⁰

Participants in enhancement trials are not medically vulnerable in the same way as ill patients, but neither are they equivalent to healthy volunteers who participate in research for altruistic reasons or for compensation. Of particular concern is whether a type of “therapeutic misconception” functions in the context of enhancement research. The therapeutic misconception causes ill participants (and sometimes also investigators) to confuse research and treatment and believe that the research is designed to provide individual benefits to the participants.⁷¹ People who participate in enhancement research likewise may believe that they are in need of the intervention and have a difficult time separating enhancements provided outside of a research context with those provided as part of a protocol. The therapeutic misconception may make it difficult to get participants to understand a variety of features of the research design (e.g., randomization and double blind) and may undermine attempts to get true informed consent. There are few “cures” for the therapeutic misconception and it can be particularly difficult to overcome in some cases. For enhancement research, the key may simply lie in recognizing this type of vulnerability and making additional effort in the context of disclosure regarding the role of research.

There is no reason to think that cognitive or communicative vulnerability differs for enhancement research, although we might wonder whether participants with certain problems, such as the body dysmorphic image describe above would be considered competent to consent to participate in an enhancement study. But even if enhancement does not create any new concerns about cognitive impairment, should incompetent individual been rolled in enhancement research? The federal regulations allow legally authorized

representatives to consent to research participation for incapacitated participants. Although specific regulations for these participants have been suggested in the past, thus far none have been accepted.⁷² Numerous commentators and commissions have proposed specific guidelines and the details will not be repeated here.⁷³ Suffice it to say that enhancement research raises some unique concerns for these vulnerable participants. Who should function as legally authorized representative for enhancement research? In some cases the spouse or family may have conflicts that render them inappropriate decision makers for enhancement interventions. These conflicts may not be limited to enhancements. Consider the example of deep brain stimulation causing personality changes (there are anecdotal cases of gambling and sartorial behavior).⁷⁴ Treatment teams struggle with the role of the family in these cases, particularly if the patient is happy with the current setting but lacks insight into the personality changes, and the family is unhappy with the changes. There are studies that show that family members are not particularly good at making surrogate decisions in a treatment context⁷⁵—this maybe more problematic in an enhancement context where there is no medically recommended course of action.⁷⁶ Even more disturbing are studies that show that surrogates are sometimes more willing to consent to participation in research for another person, then they might be for themselves.⁷⁷ These concerns might lead us to be want to limit surrogate consent for enhancement research. Paradoxically, however, this might restrict from participation a number of individuals who are likely to use the enhancements and thus will be important to study, such as children.

Institutional vulnerability, or vulnerability because of institutional pressures, will be a significant issue for certain groups. For example, military personnel might be pressured to participate in research trials of a variety of enhancements. The same may be true for students, and also for athletes, whether part of a school or professional team. Headlines abound with doping scandals in sport and these individuals may well be approached to participate in research testing new ways to enhance performance. Individual and group pressures to do well in a variety of contexts have already led to the use (or misuse) of enhancements in these situations of institutional vulnerability. These groups may already be vulnerable to requests to participate in research, but may be especially vulnerable in the context of enhancement studies where the pressure to participate comes from both external sources and from internal motivation to succeed. The usual suggestion to limit the influence of institutional authority when obtaining consent wont necessarily mitigate the internal pressures and we might need additional safeguards for these vulnerable groups.

It is unclear whether deferential vulnerability (which focuses on informal, rather than formal hierarchies) will be a concern for enhancement research. Deferential vulnerability may occur due to gender differences (e.g., women may be subordinate to men) or professional roles (e.g., patients may be subordinate to physicians). Certainly in some enhancement contexts, such as cosmetic surgery, we may be particularly concerned about the effects of deferential vulnerability in the informed consent process.

Economic vulnerability is likely to play a similar role in the enhancement context as in more traditional research and thus the usual protections around exploitation and undue influence should function.⁷⁸ Likewise, social vulnerability may not be any greater a problem, although perhaps stereotyping will be a concern. There is evidence that the way in which information is framed makes a significant difference in the likelihood that consent will be obtained.⁷⁹ Investigators are as subject to stereotyping and prejudice as are other people. How might this be particularly problematic in an enhancement context? Take the example of double eyelid surgery that is done most often on Asian women seeking to have folds put into their eyelids to make them appear more “westernized.”⁸⁰ The individuals seeking this surgery claim that the lack of folds makes them look “dull” and “passive.”⁸¹ Would an investigator who studies this type of procedure be “buying into” the stereotype? Should we be concerned

about the informed consent dialogue involving an investigator who agrees with the stereotypes? Or an investigator who does not agree, but invokes the stereotype to promote subject recruitment? We may need to be careful about designing studies involving socially vulnerable populations which appeal to underlying stereotypes. For example, a study designed to explore racial differences in cognitive enhancements might be of particular concern. NBAC suggests community involvement in the study planning process, although their concern is more with placing the burdens of research unfairly on undervalued social groups, then with the impact of stereotyping.⁸² In some cases IRBs might take steps to safeguard the informed consent dialog by insisting on neutral-third parties to facilitate disclosure. In other cases, we might have to accept the presence of underlying stereotypes and make efforts to limit risks and to educate investigators and others who will be part of the consent process.

Although some of the issues raised by, and responses to, vulnerability may be similar, the populations deemed vulnerable might be different in the context of enhancement research than in the context of health-oriented research. Employers interested in boosting worker productivity may pressure employees to enroll in enhancement trials. Athletes may feel compelled to participate in studies of performance-enhancing biotechnologies. Members of the military may be required to serve as subjects in studies of interventions to enhance their war fighting abilities. Moreover, for those groups that are already considered especially vulnerable in a traditional research context, such as incapacitated adults, children, fetuses, and embryos, enhancement research may raise additional concerns.

D. A Brief Note on Children

Crafting ethical guidelines to protect human subjects in biomedical enhancement research is likely to be complex and controversial. Yet it is critical in view of the burgeoning amount of this type of research that can be expected in the future. We've focused on evaluating risks and benefits and obtaining informed consent in adult populations, but it will also be important to consider how to protect children. This is a large topic that we are addressing in a separate paper. However, a few brief observations may be useful here.

Parents can be expected to try biomedical enhancements on their children, and indeed are already doing so in the form of giving methylphenidate and dextroamphetamine to children who do not have a diagnosed attention deficit.⁸³ The Common Rule gives children special protections in research, but it is not clear how these provisions would apply to enhancement research with children, or whether they would provide adequate protection. Additionally, there may be concerns raised by enhancement research that reach beyond the current regulations and may prompt us to consider ethical issues in human subjects research more generally. For example, some enhancement studies may require extremely long-term monitoring if the enhancement results in permanent changes. How do you evaluate the risks and benefits and obtain consent for what might be a life-long research study? There are similar issues raised for other studies, such as xenotransplantation⁸⁴ and gene therapy trials, but those cases involve treatments for individuals who may already be familiar with long-term medical monitoring (and may need to continue that for reasons of illness). Enhancement studies, by contrast, involve healthy individuals who may be less able to understand the implications of their initial choice to participate.

E. Conclusion

As new treatments are developed for diseases, there will be interest in using some of the technologies in healthy populations to enhance performance. How and whether these new uses can be studied will depend in part on whether the federal regulations provide adequate protections for human participants.

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46. 21 C.F.R. 50...
47. There are few exceptions to the documentation requirement. 46 C.F.R. 117.
48. 45 C.F.R. 46.116(a)
49. Subpart B of the HHS guidelines.
50. Subpart C of the HHS guidelines.
51. Subpart D of the HHS guidelines and 21 C.F.R. 50.50.
52. 45 C.F.R. 46.111(b).
53. Juengst p. 4. Expertise does not refer to the ability of a specific physician to do a specific kind of procedure, but instead to whether the intervention is part of the practice of medicine. Thus we would not expect or require a traditional informed consent discussion in a situation where a physician happens to be offering haircut services to his patients. Physicians can claim no special expertise in offering haircuts (although perhaps the physician in question is also trained as a barber). The point is that when we imagine the paradigm situation in which informed consent operates, the assumption is that the intervention is one for which a physician has special expertise, and thus a physician has an ethical and legal obligation to provide information to the patient/subject about the intervention in question—this is one of the primary reasons for placing a disclosure obligation on the physician.
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56. Berg et al., at 58–60.
57. See, e.g., FDA Breast Implant Consumer Handbook. 2004 accessed July 18, 2007 <http://www.fda.gov/cdrh/breastimplants/handbook2004/localcomplications.html>
58. For example, the INAMED breast implant brochure includes in the list of benefits: “may result in a more flattering, better proportioned figure, more clothing options, and may enhance your confidence and self-esteem.”
59. There is a broader question about how to weight individual versus societal risks and benefits. This is addressed in greater detail elsewhere. CITE to long-range risk paper.
60. But see Emanuel’s argument that nothing really coercive.
- 61.
62. CITE
63. 45 CFR 46.111(2)
64. Consent requirement may also be altered under 45 C.F.R. 46.116(c), which refers to research studying public benefit programs. However, neither the exceptions in (c) nor (d) apply to research involving “nonviable neonates”. 45 CFR 46.205(c)(5).
65. For a more complete discussion of deception research see Levine, Robert. *Ethics and Regulation of Clinical Research*. 1986:221–228.
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69. National Bioethics Advisory Commission. *Ethical and Policy Issues in Research Involving Human Participants*. 2001:85–92.
70. *Id.*
71. Berg et al., at 288–290.
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Biography

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