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Regulatory and Ethical Principles in Research Involving Children and Individuals with Developmental Disabilities

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Abstract

Children and individuals with developmental disabilities (DD) compared to typical participants are disadvantaged not only by virtue of being vulnerable to risks inherent in research participation but also by the higher likelihood of exclusion from research altogether. Current regulatory and ethical guidelines although necessary for their protection do not sufficiently ensure fair distributive justice. Yet, in view of disproportionately higher burdens of co-occurring physical and mental disorders in individuals with DD, they are better positioned to benefit from research by equitable participation. Greater elucidation of this ethical dilemma is called for by researchers, institutional review boards, and funding agencies to urgently redress the imbalance. This article discusses many of the regulatory principles to ensure better research participation of children and individuals with DD: human rights, validity, distributive justice, beneficence/nonmaleficence, and autonomy.

Keywords

regulatory and ethical principles; children and developmental disabilities

Although biomedical research involving children and individuals with developmental disabilities (DD) has contributed greatly to improvements in their quality of life, it is also remembered for major ethical violations. Even the thought of potential abuse is so intolerable to researchers and institutional review boards (IRBs) that the result of such abuses has tipped the scale of human rights. It may be considered more acceptable to exclude children and individuals with DD from research participation altogether. This may be understandable to avoid any possibility of professional censure, sanctions by oversight agencies, or litigation. However, a meaningful response lies in the provision of resources and specific planning for better research participation to help elucidate conditions unique to these populations (Dresser, 1996). This includes development of research funding announcements (RFAs) and other incentives by sponsoring agencies to accommodate inclusion of children and individuals with DD, rather than resignation to their exclusion as a matter of convenience, difficulty, or cost.

The Nuremberg Code (1948), the *Declaration of Helsinki* (1964) and *The Belmont Report* (1979) represent the ethical cornerstones guiding research involving human participants

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since the Nuremberg Trials. However, these documents do not offer specific guidance on research involving children and individuals with DD (Glantz, 1996; National Commission, 1979; World Health Organization & Council for International Organizations of Medical Sciences [WHO/CIOMS], 1978). The impetus for each code obviously has been to respond to different research challenges of the time, and for each, the hope has been for ethics to define the limits of human research (Emanuel, Wendler, Grady, 2000; Levine, 1994; Vanderpool, 1996). Although each code has separate sections for the inclusion of children and individuals with DD, they have not sufficiently elaborated on the specific dimensions concerned. This may not seem surprising because it has been acknowledged from the conception of these codes that providing instructions on ethical challenges unique to special populations was not a goal (Beecher, 1959; Curran, 1982; Musto, 1999; Perley, Fluss, Bankowski, & Simon, 1992).

DD is a severe and chronic disability of an individual that (a) is attributable to a mental or physical impairment or combination of mental and physical impairments; (b) is manifested before a person attains age 22; (c) is likely to continue indefinitely; (d) results in substantial functional limitation in three or more areas of major life activity: self-care, receptive-expressive language, learning, mobility, self-direction, capacity for independent living and economic self-sufficiency; and (e) reflects the person's needs for a combination and sequence of special interdisciplinary or generic care, treatment, or other services that are of lifelong or extended duration and are individually planned and coordinated (PL 100–46, 1987).

One important reason to make a closer examination of existing codes with respect to DD is precisely because past violations have occurred, and there is a need to elucidate the relevant ethical principles. For instance, as late as the 1970s in the Willowbrook State School studies, children with DD have been intentionally infected with hepatitis to follow the progression of the virus and to test the effectiveness of a hepatitis vaccine (Angell, 1992; Beecher, 1966a; Katz, 1972; Krugman, 1971, 1986; Krugman, Ward, Giles, Bodansky, & Jacobs, 1959; Ward, Krugman, Giles, Jacobs, & Bodansky, 1958). Now IRBs and ethical codes such as the International Ethical Guidelines, both established by the Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO) (WHO/CIOMS, 1978), provide the necessary oversight for all relevant studies and have considerably reduced the number of egregious ethical transgressions seen in the past (Levine, C, 1996).

Still, there is a further rationale for emphasizing the need for supporting the inclusion of specific categories of vulnerable participants such as children and individuals with DD. Unless this is done, research is unlikely to benefit groups proportionately. Recognizing this issue, many authors including the American Academy of Pediatrics (AAP) now emphasize wider research participation of children (AAP, 1995; Angell, 1992; Center for Drug Evaluation and Research, 1996; Department of Health and Human Services [DHHS], 1998, 2001b; Nelson, 1998). To date, however, there have been no well-publicized research guidelines that call for the inclusion of individuals with DD (Levine, R. J., 1996).

DEFENSE FOR MORE SPECIFIC GUIDELINES

Children and individuals with DD are uniquely vulnerable populations (Glantz, 1996). They collectively experience greater burden from emotional and mental disorders, and they receive less and poorer quality of care than the general population (Reiss, 1994).

First, the reason for distinguishing developmentally mature adults from children and individuals with DD in research participation is that the latter are ordinarily not able to make informed decisions or defend themselves (CIOMS, 1993; Glantz, 1996). It would not be

unreasonable to assume that this precise vulnerability has made them targets to promote science through unethical practices in the past. This leads to the current argument for their exclusion from research altogether. This conclusion is unsatisfactory when research performed today can be ethically defensible and when individuals stand to benefit from it (Dresser, 1996). With the promise of new developments in neurology, genetics, psychopharmacology, and other disciplines in medicine, enrollment of these individuals into studies is merited.

Second, the presentation of many disorders is modified in the presence of disability (Pearson & Aman, 1994; Szymanski & Tanguay, 1980). Compared to the general population, individuals with DD have 4 times more preventable mortality, higher rate of obesity, infections, asthma, and cardiovascular disease. Such physical and mental health disparities in incidence, prevalence, mortality, and disease burden in children and individuals with DD are seriously understudied. Mental health problems in individuals with DD are the primary reason for the failure to adapt to family, school, and community (Reiss & Benson, 1987).

Third, the use of psychotropic medications in the community care of individuals with DD is changing—it is important that research specific to this population drives this change. Investing in research in mental health aspects of DD is important also for the potential savings that such research could have in general health and other sectors (e.g., economic development, employment, housing, and social services). Despite the increasing recognition of these issues DD research remains segregated from the mainstream. A paradigmatic change in thinking is needed because the developmental perspective is fundamental for the understanding of mental disorders (Munir & Beardslee, 1999).

Finally, health issues of individuals with DD need to be viewed in the context of public health whose mission is to generate organized community efforts to address the public interest (National Institute of Mental Health [NIMH], 2001). In addition to the limited number of trained researchers interested in DD, the enrollment of individuals with DD in research protocols involving mental disorders is limited, and problems with informed consent persist. NIMH recognizes that it has a “special duty to help foster research that will advance the health and lives” of persons with DD (NIMH, 2001). The cognitive limitations necessitate an interpretation of these codes in addressing persisting ethical challenges.

POST-WORLD WAR II ETHICS CODES

During World War II, some of the Nazi experiments designed to test the boundaries of human endurance had included subjecting humans to high altitudes, freezing temperatures, malaria, mustard gas, sterilization, and poisoning (U.S. Government Printing Office, 1950). A product of the Nuremberg Trials that included the convictions of 24 Nazi Germans for conducting unethical experiments on prisoners, the *Nuremberg Code* (1948) was an important cornerstone in charting the future direction for the conduct of modem medical research.

The *Nuremberg Code* brought forth an era of enlightenment about the extent to which the human rights could be violated if unchecked. It especially highlighted the principle of autonomy and the need for informed consent, addressed aspects of validity and beneficence/nonmaleficence; the principle of distributive justice was not emphasized (Grodin, 1992).

In 1953, the World Medical Association (WMA) committee on Medical Ethics began to wrestle the problems inherent in the *Nuremberg Code’s* restrictive definition of voluntary informed consent. Because the permission to be included in research must be received from the participants themselves, some children and individuals with DD might never be able to participate in studies without violating the *Nuremberg Code* (Beecher, 1959). It was

suggested that a set of guidelines adopted by a medical guild, as opposed to a jury (as in the case of the Nuremberg Trials) could more accurately address the needed challenges (Beecher, 1960).

After 10 years of meetings by the WMA, the *Declaration of Helsinki* was adopted in 1964 primarily based on the structure established by the *Nuremberg Code* (Perley et al., 1992). It included the suggestion of seeking the informed consent of the legal representatives of the child as a proxy.

In 1974, the U.S. Congress authorized the National Research Act that created the first National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979). The Commission's task was to identify the fundamental ethical principles that should guide biomedical and behavioral research—a product of this work was *The Belmont Report.* This document was unique in that it directed investigators to consider (a) the boundaries between biomedical and behavioral research, (b) the assessment of the risk-benefit ratio, (c) the guidelines for the appropriate selection of human participants for participation, and (d) the definition of informed consent in various research settings.

A further contribution offered by the *Belmont Report* was the recognition that some of the ethical principles may conflict with one another. For example, on one hand it was advisable to protect or restrict the participation of vulnerable populations out of respect for persons. On the other hand, the principle of distributive justice emphasized that participants ought to share in the burdens and benefits of the research.

In 1978, the CIOMS and the WHO set out to establish a code for helping developing countries create methods to protect the participation of human participants. Specifically, they were guided by two main goals: to define a national policy on the ethics of medical and health research and to adopt standards appropriate to their specific local needs (Perley et al., 1992). The product of this effort was the development of the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 1993). One of the contributions established by these guidelines was a more realistic treatment of informed consent, as opposed to simply impressing researchers of its importance as the *Nuremberg Code* had achieved. The CIOMS guidelines admitted that strict adherence to informed consent may be unattainable for children and individuals with DD. To correct this limitation, it proposed conditions for the appropriate inclusion of these populations while protecting their liberties (Perley et al., 1992; WHO/CIOMS, 1982).

COMPARISON OF ETHICAL GUIDELINES

In this article we emphasize five ethical dimensions distilled from these influential codes—the *Declaration of Helsinki,* the *Belmont Report,* and the CIOMS guidelines. These principles offer a framework for researchers to consider: human rights, validity, distributive justice, beneficence/nonmalficence, and autonomy.

Table 1 compares the *Declaration of Helsinki,* the *Belmont Report,* and the CIOMS guidelines. These ethical dimensions represent a framework that researchers and IRBs ought to further consider (Beauchamp & Childress, 2001). Although the final evaluation may generate different decisions to allow or restrict researchers if given to differing IRBs (Redshaw, Harris, Baum, 1996; Royal College of Physicians, 1990; Royal College of Psychiatrists, 1990; Wynn, 1982), all final decisions must be supported by considerations of their value. The enrollment in a study needs to serve the participant directly, and a neglect of any of these basic principles may have unethical consequences (Truog, Robinson, Randolph, & Morris, 1999). It may be important for IRBs to structure the process of review with respect to each principle.

In the United States, the IRBs may not have a utilitarian orientation with respect to the principle of distributive justice that has an overriding concern of the welfare of the group over the individual. Another issue relevant in the United States pertains to medico-legal and regulatory concerns paramount for institutional protections and the protection of investigators. There is thus greater emphasis on human rights such as an individual's right of privacy and confidentiality (article 12, United Nations [UN], 1948), principle of autonomy and perhaps a relative understatement of the principles of distributive justice and validity.

On the other hand, in the developing countries with poor resources the debate has been lopsided with emphasis on the principles of distributive justice and validity. This is evidenced by the heated debate over the unethical placebo-controlled clinical trials to reduce perinatal transmission of HIV in developing countries (Lurie & Wolf, 1997; Whalen, Johnson, Okwera, et al., 1997). Although the subsequent attempts to revise the *Declaration of Helsinki* under the definition of a "local standard of care" applicable to such countries when comparing them to the United States failed (Brennan, 1999) there had been a blurring of the universal ethical principles as enunciated in the *Declaration of Helsinki* (Angell, 1997). Initially, the funding agencies in the United States had concerns about the "validity" of such studies if they were to be conducted without a control (no treatment arm). Such considerations on validity took precedence over the basic human rights when such studies would almost certainly never have been accorded permission had they been proposed to be conducted in the United States.

PRINCIPLE OF HUMAN RIGHTS

The fair treatment of children and individuals with DD—accommodated under the ethical principle of human rights—seems to be well-respected today. Currently, the public and medical communities have a greater awareness and sensitivity to questionable scientific research.

The first duty of IRBs is to ensure that human rights are vigorously protected. Although this undoubtedly applies to all participants, this is especially relevant when working with vulnerable participants such as children and individuals with DD. The elements of human rights taken from the UN's Universal Declaration of Human Rights (1948) that apply to the purposes of this article include:

1. All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act toward one another in a spirit of brotherhood (article 1).
2. Everyone has the right to life, liberty, and security of person (article 3).
3. No one shall be subjected to torture or to cruel, inhumane or degrading treatment or punishment (article 5).
4. Everyone has the right to recognition everywhere as a person before the law (article 6).
5. No one shall be subjected to arbitrary interference with his privacy, family, home or correspondence, nor to attacks upon his honor and reputation. Everyone has the right to the protection of the law against such interference or attacks (article 12).
6. Everyone has the right to the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author (article 27.2).

These are first-order principles. No research, however important it may be, is justified if it violates the rights of a single person. Although the utilitarian calculus (cf., "the greatest

good for the greatest number") on balance may save more lives (Medical Research Council, 1962–1963; Thomson, 1986), it is of foremost importance for IRBs to protect individual human rights (cf., "first do no harm"). This also holds from a distributive justice perspective that argues that research cannot burden a selected group of participants to serve others or involve only those who are available based simply on convenience (Levine, 1986). Studies should pay special attention to articles 1 and 3 (UN, 1948) with reference to the citizens of developing countries or those living in developing nations with less fortunate circumstances.

PRINCIPLE OF VALIDITY

Because researchers are more likely to understand the nature and purpose of a project better than their participants, they are responsible for being aware of the requirement of validity, which demands scientifically sound medical practices. The aims of a study must advance the understanding and treatment of a condition. In general, the study must seek to uncover uncertainty with one or more approaches to a problem that can only be resolved through experimentation (National Institutes of Health [NIH], 1998). Furthermore, research must justify the use of resources in consideration of possible risks/benefits (Emanuel et al., 2000; Levine, 1986). Research protocols should therefore have clear objectives and the potential for doing good (Lieberman, 1996; Wing, 1999). Furthermore, all investigators need to have the prerequisite scientific training that includes the ability to provide treatments, detect adverse affects, and stop experimentation (Levine, 1986; Levine, Lebacqz, 1979). Research that proceeds from these criteria is more likely to produce valuable results. In this way, future studies are better able to fully develop the findings established from previous works. Invalid research exposes participants to unnecessary risks and cannot be justified (Emanuel et al., 2000; Greenwald, 1982; Koocher, 1990; Levine, 1986; Levine & Lebacqz, 1979). It squanders time, resources, and produces data that is unfit for wide dissemination. Furthermore, patients may be harmed if misleading results are applied to future investigations (Koocher, 1990; Wing & Brown, 1970).

Most participants are unlikely to evaluate the merits of studies without assistance. Children and participants with DD are almost certainly unable to understand the relevance of experiments in which they are participants. Simple assurance to parents, or other surrogates, that studies are sound and methodical does not suffice. Moreover, this principle cannot be judged solely on the individual's ability to understand and consent to the procedures, the risks and benefits, or the usage of data. Therefore, there is a specific need for researchers and IRBs to independently evaluate the proposed research studies to ensure compliance with this principle.

A related consideration is the scientific accuracy of IRB reviews facilitated by experienced scientists. Given the increasing number of studies, the lack of regulation and the limited time of reviewers who serve on an IRB, there is a danger of inadvertently permitting research that would not be allowed under better circumstances. For instance, an invalid study may not be detected (false negative outcome of IRB review) whereas a perfectly valid protocol may be delayed on procedural problems that are not resolved because of investigator's inability to follow-up or inadequacy of resources (false positive outcome of IRB review). At best such an "error" will serve to delay the implementation of a valid study that should otherwise proceed. Unfortunately such errors are more likely to be magnified for research involving children and individuals with DD compared to other categories of participants and differentially compromises research in this area. Further resources need to be made available to ensure the principle of validity is protected to be fully effective.

PRINCIPLE OF DISTRIBUTIVE JUSTICE

The principle of distributive justice considers fair, equitable, and appropriate division of risks as well as benefits generated by a given study (Beauchamp & Childress, 2001). There are several models for distributive justice guided according to each participant's equal share, need, effort, societal contribution or merit (National Commission, 1979; Rescher, 1966; Ryan, 1978). These models may raise questions of unfairness as judgments are inevitably biased. For example, if the benefits of research are given to those who are considered to have high merit, this may suggest that achievement is more valued than individual need, effort, or societal participation. This is especially salient in research involving children and populations with DD as they are vulnerable to differential application based on a "relative value scale."

Given such pragmatic problems facing individuals living in poorer regions, a model that disproportionately values some over others may seem inevitable, however its application to research is an ethical slippery slope. These challenges further restrict the application of a fair distributive model to children and individuals with DD, or individuals living in poorer regions. Under the premise that each of us is equal, the fairest distribution is according to an equal share and need.

In general, a representative demographic population affected by a given condition should be able to participate in a study irrespective of whether the condition affects them exclusively or nonexclusively. Children and individuals with DD deserve equal participation and therefore ought not to be restricted from involvement (Levine, C, 1996). Developmentally mature adults who are able to provide consent directly should be studied first to establish efficacy and appraise risks (Grodin & Glantz, 1994). However, it can be argued that they can never be a true substitute for individuals with specific vulnerable biological or social circumstances. In fact, all beings whether they are children or individuals with DD have unique circumstances. In each category participation should be guided by choices that involve greatest chance of benefit and least likelihood of harm irrespective of such categorical distinctions (National Commission, 1979; World Medical Association, 1997). Kant once retorted that individuals are not a means but an end and, as such, they are irreplaceable, and in being irreplaceable they are different. It is through our dynamic experience, and not based simply on who we are, that we are "capable of enjoying life… capable of suffering and of facing death consciously" (Popper & Eccles, 1986). Criteria based on social, racial, sexual, and other cultural biases should not be used to discriminate who will or will not enter into studies (Beauchamp & Childress, 2001; NIH, 1998; Ramsey, 1970). On the other hand, national policies need to ensure fair research participation based on gender, age, or minority status (NIH, 1994, 1998, 2001).

PRINCIPLE OF BENEFICENCE AND NONMALEFICENCE

It is important to balance the competing claims of potential benefits and risks assumed by each participant. The *Report and Regulations: Research Involving Children* by the National Commission (1977) and the *NIH Guidelines on the Inclusion of Children as Participants in Research* (NIH, 1998) summarizes the four categories of research on children according to risks and benefits: (a) *not greater than minimal risk/direct benefit,* (b) *not greater than minimal risk/no direct benefit,* (c) *greater than minimal risk/direct benefit,* (d) *greater than minimal risk/no direct benefit* (Table 2). All of these combinations of risks/benefits are permitted, however the strength of the argument justifying each category must be stronger when the risks to participants reach greater than minimal levels and when the prospects of direct therapeutic benefits decrease (e.g., as categories progress from a to d) (British Paediatric Association, 1980; NIH, 1998). Studies that pose minimal risk to children (or

slight increase over minimal risk with justification of direct benefit to the individual child) are permitted with parental consent.

No well publicized effort has been made to support further inclusion of individuals with DD in studies involving greater than minimal risk, although similar criteria can be accorded to this group. To be sure, the obligation of investigators to minimize risks and maximize benefits is often fraught with complications despite guidelines (Beauchamp & Childress, 2001; DHHS, 1991, 2001a, 2001b). Research on children and individuals with DD is permitted and frequently requested if it holds the potential to benefit them and only if prior studies on less vulnerable participants, who are better able to provide consent, have been validated. There is no objective determination of fairness and skilled members of IRBs need to render such decisions based on considerable reflection (Dresser, 1996).

Although research that offers no immediate therapeutic benefits needs to be considered as it holds promise for the future, a favorable risk/benefit ratio is a prerequisite in all circumstances. With respect to the requirement that research presents experiences that are reasonably commensurate with a given participant's actual or expected circumstances, it needs to be said that participants ought to have a say in refusing further participation at any stage of the research based on their subjective experience of risk or discomforts, especially in research that involves no therapeutic benefits. Nontherapeutic research is generally not ethically justified when it involves more than minimal risk and when the primary aim is the acquisition of knowledge for other pediatric participants. An example is the use of "normal" controls in procedures where they have no direct gains but face discernible risk, pain, and discomfort (Munir & Earls, 1992).

PRINCIPLE OF AUTONOMY

The principle of autonomy involves informed consent, protection of privacy, and confidentiality. The regulatory procedures allow participants (or their legal representatives) to express their free will with respect to the various dimensions of the research. These include risks/benefits, alternative treatments, exit procedures, study objectives, conflicts of interests, affiliations and funding sources (Alderson, 1995; Beauchamp, 1989; Beauchamp & Childress, 2001). Children and individuals with DD are generally unable to give free informed consent and require special protections (Angell, 1988; Barry, 1988; Keith-Spiegel, 1976). The pediatric guidelines for informed consent have been described in the National Research Act (1974). Informed consent in pediatric research means permission of parents (biological or adoptive) or other legal representatives or "guardians" (individuals authorized under state or local law to consent on behalf of the child). As a general rule in research involving minimal risk it may be sufficient to obtain the consent of one parent. In research involving greater than minimal risk, the permission of both parents needs to be sought whenever available (DHHS, 1991; Munir & Earls, 1992; NIH, 1998).

In addition to requiring informed consent by a parent or other legal guardian, the regulations make adequate provision for soliciting assent from the mature child or adolescent participants directly. This choice is important for older children and adolescents, particularly if the research involves no direct benefit to them. The IRBs define assent guidelines by taking into consideration the age, maturity, and the psychological state of the children.

A signed parent consent form alone is not sufficient to establish the process of consent, nor does it provide protection from liability. The process is enhanced by the use of clear, simple, and age-appropriate language in materials given to parents, children, or adolescents. In addition, parents need to be allowed adequate time to discuss the project with family or friends to make thoughtful decisions about participation (Munir & Earls, 1992).

The informed consent is obviously complicated whenever participants have diminished mental capacity. Individuals with DD who are unable to fully understand the scope and implications of the proposed research cannot give informed consent. If such informed consent cannot be obtained because of a person's diminished autonomy, it might be assumed that no research could ever be performed on participants with DD. It may then be argued that it is improper even to seek informed consent from these individuals (Beecher, 1959). Yet the reality of these situations is never so absolute. It has been shown that many children and individuals with DD have an understanding of the consequences and implications rather than a complete lack of understanding (Keith-Spiegel, 1976; Weithorn & Campbell, 1982). The IRBs, therefore, share the obligation to assist the investigators to bring vulnerable participants closer to the informed consent process.

We argue that the inability of vulnerable participants to provide complete consent represents a constraint on their freedom. These individuals are unable, with no fault of their own, to realize the full value of their rights. Although the IRBs are concerned of the potential for abuse and legal implications of failure to protect such participants, they have a further ethical obligation to make sure that such participants receive the benefit of inclusion in research that may otherwise be beneficial to them. To the extent that participants are able to understand the research and IRBs are satisfied that a process has evolved to protect vulnerable participants from potential abuse, research participation may be possible. Vulnerable participants who decline participation on volitional grounds because of arbitrary reasons should always be allowed time to air their objections and not be included against their will (Graham, 1999).

The elements of a vulnerable participant's legal representative's proxy consent must include a full understanding of all the risks and benefits and alternative choices available to the participant. The assumption is that a legal representative will act foremost in the interest of the participant (Rawls, 1999). When enrolled in a research project, some vulnerable participants may demonstrate an unwillingness to participate. In such circumstances researchers must reconsider overriding any prior consent arrangements.

Pain can be used as a universal indicator of withdrawal of consent among people with diminished mental capacity. Some research participants may feel obligated to continue despite the pain for fear of losing face or being rejected from care. It is precisely such circumstances that make them vulnerable, and researchers need to monitor such "willingness" as well as unwillingness to continue (DHHS, 2000). To be sure, the perception of pain is often a subjective one. Senses can deceive, and experiences depend on a person's state, for example, mood, alertness, or overall health. It may be reasonable to assume that investigators should refrain from making outright judgments in claiming knowledge about an individual's feelings (Curley, 1978; Montaigne, 1957). Still, experimentation should be stopped when pain is indicated in participants.

CONCLUSION

The history of biomedical research over the past 50 years has shown that children and individuals with DD represent populations that are especially vulnerable to human rights violations. As discussed in this article, codes that govern research on human participants do not yet apply with equal force to such vulnerable groups and special ethical challenges remain.

More research is clearly needed involving vulnerable participants as a matter of ethical obligation, and only their inclusion is paramount for achieving this goal. Yet we recognize that the ethical issues are often amplified when working with children and individuals with

DD and complicated by their inherent limitations for informed consent. In view of this lack of understanding, what is ethically permissible for more developmentally mature participants is considered unacceptable for persons with diminished mental capacities. Informed consent by parents and legal representatives is not always feasible. Finally, the very procedures that can be used to provide informed consent may fail.

Anticipating all these issues, the advent of the IRBs and the regulations that govern them have effectively halted the possibility of intentional abuses of basic human rights. Such outright violations involving vulnerable participants are much less likely to occur in today's research. Furthermore, significant advances in investigator training and the media presence in exposing questionable research practices to a conscientious public make adverse outcomes less likely (Pappworth, 1967).

By providing a discussion of the ethical principles that govern research involving vulnerable participants, we further hope to facilitate affirmative inclusion of such participants in research in the future. In today's climate, however, the IRBs may be placing a greater emphasis on strict implementation of informed consent rules. Yet as discussed earlier, the informed consent is not a homogeneous process. We agree with Beecher (1966b) that many children and individuals with DD do have a partial understanding of the consequences and implications of research. IRBs and most particularly funding agencies with explicit RFAs have a responsibility to promote participation of vulnerable participants in research studies rather than distancing them through a narrow interpretation of informed consent definition. *The parens patriae* doctrine (Cantor, 1973) by legal guardians and IRBs should not only work in the direction of protection by exclusion, but by protection through inclusion. Often the risks are minimal, and the arguments that such participants are unable to consent are overstated. Furthermore, the conflicts of commitment by IRBs also may inadvertently prioritize institutional precautions and legal concern.

New and more specific provisions for appropriate inclusion of vulnerable participants are necessary that define procedures for monitoring and withdrawal of consent as necessary. Such an open door policy with a less restrictive approach is necessary to facilitate research on this highly neglected area. Although increasing regulations may discourage some investigators in reaching out to vulnerable populations, the innovative leadership by National Institute of Mental Health (NIMH) in its strategic plan on mental health disparities is most encouraging with a specific policy to help underrepresented groups (NIMH, 2001). As it stands, urgent action is needed as most children and individuals with DD receive less mental health care, poorer quality of care, and are underrepresented in mental health research.

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TABLE 1

Comparison of the *Declaration of Helsinki* (1964), the *Belmont Report* (1979), and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993)

Ethical dimensions	DH[a]	BR[b]	IE[c]
1. Human rights *(Universal Declaration of Human Rights*, United Nations, 1948)			
The fundamental prerequisites for human well being where each can achieve his/her full potential			
a. All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act toward one another in a spirit of brotherhood (article 1)	++	++	+
b. Everyone has the right to life, liberty, and security of person (article 3)	+	+	+
c. No one shall be subjected to torture or to cruel, inhumane or degrading treatment or punishment (article 5)	−	+	+
d. Everyone has the right to recognition everywhere as a person before the law (article 6)	++	+	+
e. No one shall be subjected to arbitrary interference with his privacy, family, home or correspondence, nor to attacks upon his honor and reputation. Everyone has the right to the protection of the law against such interference or attacks (article 12)	−	−	−
f. Everyone has the right to the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author (article 27–2)	++	−	++
2. Validity			
Accuracy and closeness to the stated scientific goals			
a. Have a clear objective	−	++	++
b. Have a good research design	++	−	+
c. Be feasible and executable	++	++	−
d. Be carried out by competent researchers	++	−	+
e. Be conducted according to scientifically accepted best practices and in a methodologically rigorous manner	++	+	++
3. Distributive justice			
The fair distribution of research benefits and risks			
a. Inclusion of subjects for conditions that affect their group	+	+	+
b. Exclusion of subjects for conditions that affect their group	+	+	+
4. Beneficence/nonmaleficence			
The obligation to maximize benefits and minimize risks			
a. Minimize (direct) risks to the individual	+	+	+
b. Maximize (direct) benefits to the individual	+	+	+
c. Assess the overall usefulness and value of the research for the participants	+	+	+
5. Autonomy			
The permission granted by subjects to allow research			
a. Informed consent obtained by subjects or their guardians	++	++	++
b. Informed assent obtained by subjects if they are unable to give consent	++	++	++

Note

[a] DH = The *Declaration of Helsinki:* This code was written in 1964 by the World Medical Association and has influenced the creation of the first Institutional Research Board.

[b] BR = The *Belmont Report:* Drafted in 1979 by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, the code must be read by all researchers involved in human experimentations.

[c] IE = International Ethical Guide-lines for Biomedical Research Involving Human Subjects: Developed by two international health organizations, these guidelines have established how the principles in the *Declaration of Helsinki* could be applied to research in developing nations.

++ Included. + = Implied. − = Not included.

TABLE 2

Additional Requirements for Research Involving Children as Human Subjects

	Risk gradient	
Benefit gradient	**Not greater than minimal risks**	**Greater than minimal risks**
Prospect for direct therapeutic benefit	*(a) Not greater than minimal risk/Direct benefit* Assent of child and permission of at least one parent	(c) *Greater than minimal risk/Direct benefit* Assent of child and permission of at least one patent; Anticipated benefit justifies the risk; and Anticipated benefit is at least as favorable as that of alternative approaches
No prospect For direct therapeutic benefit	(b) *Not greater than minimal risk/No direct benefit* Assent of child and permission of at least one parent	(d) *Greater than minimal risk/No direct benefit* Assent of child and permission of both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child; Only a minor increase over minimal risk; The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; and The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition.

Note.

[a] NIH, 1998; Title 45 CFR 46, 1991.

[b] NIH, 1998; DHHS, 1991.