REFERENCES

Voluntariness

OF CONSENT TO RESEARCH

A Conceptual Model

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A good deal of policy and practice in human subjects research aims to ensure that when subjects consent to research, they do so voluntarily. To date, however, voluntariness and its impairment have been poorly conceptualized and studied. The legal doctrine of informed consent could provide a useful model.

Informed consent to research derives from a legal doctrine that calls for potential research subjects to have meaningful choice. It comprises three elements: relevant *information* is provided to a person who is *competent* to make a decision, and who is situated to do so *voluntarily*.[1] The first definitive statement of the importance of consent as a prerequisite to research participation, the tribunal's decision in the Doctors' Trial at Nuremberg, underscored the crucial role of voluntariness in that process: "The voluntary consent of the human subject is absolutely essential."[2] However, existing literature on informed consent has focused extensively on the information disclosed and how well it is communicated—and, more recently, on the theoretical and practical aspects of the assessment of decisional competence—while the nature of the requirement of voluntariness has yet to be fully explored.[3]

Current controversies over the extent to which a variety of recruitment approaches may compromise voluntary consent to research have raised concerns about the topic. Such concerns are usually invoked under the rubrics of coercion or undue influence. The federal regulations on human subjects research refer to both concepts but define neither.[4] However, the regulations identify several subject groups—including children, prisoners, pregnant women, mentally disabled persons, and economically or educationally disadvantaged persons—as "likely to be vulnerable to coercion or undue influence." They also indicate that a criterion for institutional review board approval of such research is that "additional safeguards have been included in the study to pro-

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tect the rights and welfare of these subjects."[5]

Potentially impaired voluntariness has also been raised as an issue in numerous other contexts in the bioethics literature on consent to research. These include, but are not limited to, when:

1) substantial monetary or other compensation is offered in exchange for entering a research study;[6]

2) subjects are recruited by their own physicians or in facilities where they are receiving care and may be hesitant to antagonize caregivers by refusing to participate, especially if they are poor, elderly, or suffering from chronic conditions;[7]

3) subjects are being recruited from traditional societies in international research and are thought to be wholly subordinate to a person in a position of authority (for example, a husband or tribal leader);[8]

4) drug abusers are recruited for studies that involve the administration of their drug of choice or are paid for participation and thought likely to use the money to purchase drugs;[9]

5) involuntarily committed psychiatric or substance abuse patients are recruited for research;[10] and

6) patients who otherwise lack access to medical care are invited to participate in studies that promise treatment for their conditions.[11]

A good deal of policy and practice regarding human subjects research has been based on assumptions regarding situations that may impair voluntariness. Many IRBs have policies that limit the amount of compensation that can be offered to subjects, although compensation practices vary widely even within the United States, and investigators are often not allowed to advertise the amount offered.[12] Some have suggested that physicians not be allowed to recruit their own patients as subjects, especially for studies involving more than minimal risk, and anecdotal evidence suggests that some IRBs may already bar this practice. Federal regulations sharply limit the kind of research that can be conducted in prisons, mandating rigorous review even for permitted categories of investigations, such as minimal risk studies of criminal behavior and incarceration.[13] Other limitations are placed on research with pregnant women and children.[14] And a variety of protections have been suggested for subjects in international and drug abuse studies, which now receive more careful review, in substantial part because of concerns about coercion.[15] However, various critics have suggested that almost all of these policy initiatives are unnecessary or overly paternalistic.[16]

Determining exactly how necessary and useful these efforts are to protect the voluntariness of consent requires a valid way of conceptualizing voluntariness and a reliable means of assessing it. The development of just such a widely accepted conceptualization of decisional competence, and the subsequent creation of instruments that allow its assessment, has opened up research on competence and allowed more informed policy discussions.[17] Until this point, however, there has been limited conceptualization of what constitutes voluntariness to consent to research (although there is helpful work on voluntary choice in other contexts), and empirical studies, for reasons we explore below, have been difficult to design and conduct.[18] Hence, regulation of the consent process has necessarily been based on a number of presumptions about conditions that may impair voluntariness, but few data exist to support either the underlying assumptions or the effectiveness of the remedies chosen.

In response to this situation, this article, after reviewing the empirical literature on voluntariness of consent to research, offers a model of voluntariness rooted in the doctrine of informed consent, describes the constraints on voluntariness that may appear in the research setting, suggests a research agenda to advance our understanding of voluntariness in practice, and indicates how the proposed model might be operationalized to detect problematic restrictions on voluntariness in consent to research.

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Studies of Voluntariness

Only a relatively small body of data exists on voluntariness and its constraints in research, and the conclusions that can be drawn from the literature are limited. This is because no two studies used the same methods, and few employed instrumentation whose reliability and validity are well established. Several studies from Africa and Asia reported that many subjects believed they were not free to make participation decisions

or to withdraw from the study.[19] Although troubling, these data do not indicate whether these beliefs derive from confusion among the subjects or from intentional behavior by researchers.[20] When a question about the source of pressure was asked directly in another African study, 6 percent of respondents cited pressure from the research team, 5 percent from other doctors or nurses, and 4 percent from health center staff. However, no subjects said that this pressure led them to believe that they could not refuse to participate.[21] Comparable data from Thailand showed that no subjects reported pressure from the research staff, and just 2 percent from their doctor or clinic.[22] In one of the few studies of voluntariness conducted in the United States, researchers looking at adolescents asked to consent to a research interview in an emergency room found that more than three-quarters of the subjects felt they had consented freely.[23] Finally, a study of research participation among thirty prisoners showed only one who reported being threatened or forced to participate in a questionnaire study, and all felt that they had made the final decision themselves.[24]

The impact of financial incentives has been examined by several research groups. A study of pharmacy students found that levels of both monetary incentives and risk influenced decisions about hypothetical enrollment in a study. Also, when higher incentives were at stake, these respondents indicated less willingness to tell investigators about restricted activities that might result in their exclusion from the protocol.[25] A similar hypothetical study with subjects recruited from a hypertension clinic also showed an impact of risk and incentive levels on projected decisions, as well as an effect of a placebo condition.[26] Neither study found that incentive levels had an impact on perceptions of risk, and both concluded that incentives influenced but did not distort the decision-making process. Another study asking members of a jury pool to imagine the impact of a five hundred dollar incentive to participate in a study of antihypertensive medication, both on their decisions and on the decisions of other people, found that most respondents believed other people would be influenced by the payment, but that they themselves would not be.[27]

All of those studies were of subjects faced with hypothetical choices. In the only set of in vivo experimental studies to date of which we are aware, investigators looked at the effect of a range of monetary incentives ($10–$160) on rates of follow-up by substance abusers. They concluded that although attendance at follow-up improved, there was no evidence that higher payments unduly influenced their decisions.[28] Whether more substantial sums might have had a more problematic impact on their decision-making is unknown.

In sum, studies to date of voluntariness in research settings—although they have contributed to our understanding of the complexities of the concept—leave substantial questions to be answered about the nature and extent of constraints on voluntariness, and in particular about the impact of offers and pressure on subjects' perceptions and decisions. Empirical data have contributed little to refining the concept of voluntariness or to fashioning reasonable public policy. Institutions and IRBs have therefore developed "rules of thumb" regarding such issues as the permissible incentive payments to subjects with little empirical footing, and apparently with substantial variation.[29] If this situation is to change, a good starting point would be to develop a clearer model of voluntariness and a typology of the ways in which it may be impaired.

Conceptualizing Voluntariness and Its Constraints

Voluntariness has been the subject of inquiry in a variety of disciplines, including philosophy, cognitive psychology, neuroscience, and law.[30] Philosophy of mind has long been preoccupied with the question of how mental events can trigger physical acts, which would appear to be a prerequisite for voluntary action.[31] Psychological and neuroscience studies in recent decades have challenged traditional notions of conscious control of behavior by identifying unconscious mechanisms that appear to initiate action before a person is aware that an act is about to take place.[32] In this view, rational explanations for behavior are epiphenomenal—in other words, they reflect after-the-fact attempts to justify actions that are simply not susceptible to conscious control.

Legal scholars and jurists, however, have generally taken a very different approach to conceptualizing voluntariness.[33] The law to date has largely avoided the conundrum created by the recent findings regarding the primary role of unconscious determinants of behavior—namely, that if no behavior is the product of conscious choice, then no act can be said to be voluntary—by focusing on whether a choice reflects the decision-making of the person in question, regardless of the process (conscious or unconscious) by which the decision was reached. Thus, for legal purposes, a decision is presumed to be voluntary if no evidence exists that someone else has unduly influenced it or coerced the person deciding. This approach is reflected in many areas of law. The Restatement of Torts, an authoritative compilation of the principles of tort law, states the general legal rule that "consent is not effective if it is given under duress."[34] Similarly, wills are invalid if the testator was subjected to undue influence,[35] criminal confessions are inadmissible if coerced,[36] and contracts entered into under duress are voidable.[37] The Nuremberg decision explicated the requirement of voluntariness by insisting that the subject "should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form

of constraint or coercion."[38] There has been a remarkable paucity of litigation that tests this principle in the context of informed consent, but commentators are agreed on the general rule.[39]

That a decision is based on the choice of the research subject himself or herself, however, does not mean that it cannot be influenced by a variety of factors, including preexisting characteristics of the individual deciding, aspects of his or her situation, and the desires and actions of third parties. Indeed, it would be difficult to envision a decision that is completely uninfluenced by any of these factors, and in any event the law does not require this.[40]

Common influences on the decisions of research subjects regarding participation in studies include the subject's preexisting values and preferences (for example, altruistic impulses to advance knowledge of a particular disorder or treatment), his or her psychological state (for example, desperation at a lack of treatment options for a life-threatening condition), legal pressures (for example, a court order for a substance abuser to get treatment that can be satisfied only in a research context), the opinions of others (such as physicians and family), and available resources (for example, lack of health insurance coverage, leading a patient to consider free treatment as part of a research study).[41] Additional considerations—such as an expectation of medical benefit, financial and other incentives, and curiosity about the process and outcome of a research study—may also influence subjects' decisions.[42] However, none of these influences necessarily means that a decision to participate in research is not voluntary.

Rather, as implied by the bodies of law noted above and as reflected in the Nuremberg tribunal's judgment, a decision is involuntary only if it is subject to a particular *type* of influence that is external, intentional, illegitimate, and causally linked to the choice of the research subject. By external, we mean that the influence must come from outside the person. Internal determinants such as confusion, fear, or unreasonable hope may result in a decision that is incompetent or unwise, but they do not render a choice involuntary.[43] This principle is exemplified in a U.S. Supreme Court ruling upholding the confession of a defendant who argued that he had been coerced by hallucinatory voices telling him that he should confess to a murder because he offered no evidence that the police had engaged in coercive behavior.[44]

However, even external influences do not negate voluntariness unless they are intentional. That is, they must result from the deliberate action of another person who intends to influence a subject's choice. Situational constraints—such as poverty, the lack of alternative treatment options, or the organizational culture of an institution or workplace—may have a profound influence on subject choice, but with the possible exception of some extraordinary cases, they do not make the choice involuntary.[45] Were we to conclude otherwise, vast numbers of people (including all poor people and all academic medical center employees) would be excluded from making decisions about research participation—a conclusion incompatible with our society's general commitment to the autonomy of the individual.[46] However, situational constraints may set the stage for intentional efforts to influence decisions (including intentional manipulation of the situation created by the constraints) and may make intentional efforts both easier to engage in and harder to detect in certain contexts, such as in hierarchical organizations, prisons, and other "total" institutions that control all aspects of a person's life.[47]

Of course, many people intentionally influence the treatment or research decisions of others. Physicians encourage patients to consent to research studies, and family members may urge potential research subjects not to enroll in a clinical trial. The impact of such influences on voluntariness is not of concern unless these influences are also illegitimate—that is, the person exerting the influence does not have the right to act in this way according to generally accepted moral norms. A spouse may have the right to say, "Unless you get treatment for your drinking problem by entering this research study, I'm leaving," since spouses are generally free to terminate marital relationships and are given considerable latitude in influencing each other's behavior.[48] A treating physician, however, does not have the right to say, "Unless you agree to enter this research project, I will no longer care for you"; having assumed responsibility for a patient's care, the physician owes a duty of fidelity to the patient's interests.

Finally, to invalidate a decision, an influence must be causally linked to

The presence of influences does not mean that a decision is not voluntary. A decision is involuntary only if it is subject to a particular type of influence that is external, intentional, illegitimate, and causally linked to the choice of the research subject.

the subject's choice. If a person exerts illegitimate external pressure on a subject to consent to research participation when the person was inclined to participate anyway and intended to accept the offer, the voluntariness of the subject's decision is not negated. Applying such pressure may be reprehensible, but since it is not causally related to the decision, it does not render the decision involuntary. As a corollary, the mere fact that an influence affects a subject's decision does not mean the decision is involuntary, so long as the influence was internal, unintentional, or legitimate.

This conceptualization of voluntariness and the circumstances that negate it is in most respects compatible with the formulation that Ruth Faden and Tom Beauchamp introduced twenty years ago in their discussion of the related concept of coercion.[49] It differs markedly, however, from the approach of Laura Weiss Roberts, who defines what she calls "voluntarism" as "ideally encompassing the individual's ability to act in accordance with one's authentic sense of what is good, right, and best in light of one's situation, values, and prior history."[50] In Roberts's view, a subject's developmental stage, illness-related symptoms, psychological issues, and cultural and religious values, as well as the complexity of the decision and a variety of contextual factors, can all limit voluntarism. Based on a view of decision-making that posits an "authentic" choice existing independently of the varied influences that impact a person at any point in time, this formulation does not reflect the law of informed consent and could not be implemented in a research setting.

Constraints on Voluntariness in Research Settings

How can we categorize the types of behaviors that may render a decision about research participation involuntary? Our classification of such constraints draws from the work of sociologist Talcott Parsons, who conceptualized the mechanisms by which one person can exert influence on the decisions of another.[51] Parsons noted four means by which influence may be exercised: appeal to shared values, inducement, persuasion, and force (which Parsons called "deterrence").[52] In the context of research, the influence of shared values may be exemplified by appeals to the impulse for altruism, inducement by offers to provide incentives, persuasion by the application of interpersonal pressure or by an exhortation to self-interest or community norms, and force by nonconsensual intervention or the issuance of threats. Appeals to common values, if honestly framed, are unlikely to constitute illegitimate constraints on choice, but the other categories can be more problematic.

Inducement to enter a research project will usually involve an offer. The *Oxford English Dictionary* defines offers as "expression[s] of intention or willingness to give or do something if desired"; in the decision whether to enter research, they are typically promises to provide a benefit to which a person is not otherwise entitled. Although offers are external, intentional efforts to influence a person's behavior, insofar as they expand a person's options without constraining choice (since people are free to choose whether to accept an offer), they are usually legitimate and do not render a decision involuntary.[53] Researchers commonly offer incentives to potential subjects, including money, free medical care or medication, and more intensive follow-up or diagnostic procedures.[54] For socially isolated subjects, the prospect of regular, supportive human contact as part of research participation may in itself constitute a significant offer. Indeed, the attractions of participating in a given study—that is, the nature of the offer—may differ depending on the subject's situation and perspective. The prospect of a lengthy hospitalization might be a disincentive for some subjects yet constitute an appealing offer to others.

An example drawn from our recent study of voluntariness of consent to research will help make this point clear. We interviewed eighty-eight participants in a variety of clinical trials at a major academic medical center. Consider a thirty-eight-year-old man who was interviewed shortly after agreeing to participate in a study of treatment for cocaine abuse. After using cocaine for roughly a decade, he was kicked out of the house by the mother of his daughter and had been rotating his residence among a number of friends. He saw the study, which involved several weeks of hospitalization, as a way to get out of his current situation—a time to change locations and to clear his head. Since he had been unemployed for the past five years, he was also attracted by the prospect of receiving $1,100 for his participation.

Offers, however, may not be entirely unproblematic. If an offer is substantial enough to undermine a person's decision-making process—in other words, if it leads a person to ignore or undervalue the risks of research participation—most commentators (with some exceptions[55]) would consider the offer to be exerting undue influence, and hence illegitimate. There is no consensus regarding the point at which an offer crosses that threshold; indeed, there is probably no universally valid way of identifying such a point since, for any individual, it will vary depending on financial status, health insurance, access to alternative treatments, and other considerations. Thus, determining the possible subject's own perspective is essential, even though prospective review of research protocols inevitably depends on estimating the likely responses of reasonable persons in the anticipated situations of the study's subject pool. Investigators, IRB members, and bioethicists expend a good deal of effort defining the acceptable limits of offers for research projects. But, even after the fact, since subjects often have a variety of reasons for enrolling in a study, it can be difficult to determine

whether an incentive has induced them unduly.

As another example, consider a forty-two-year-old unemployed man who, eight weeks into a study of treatment for opiate abuse, rated the five hundred dollars that he would receive over the course of a year as the most important factor in his decision to participate. He gave the study a score of five on a ten-point scale gauging risk and discomfort, noting that at times he'd had a bad reaction to the medication, including rashes. However, the money he would receive played a significant role in making it worthwhile to accept these adverse effects. But he also cited getting badly needed help for his addiction, free treatment, and the reputation of the treatment facility, among other factors, as having a substantial effect on his decision.

Persuasion, as Parsons uses the term, can involve appeals to self-interest (for example, "If you agree to this innovative surgical trial, you may heal and be back at work more quickly" or "If you enter this clinical trial, you may receive a new medication not yet generally available that may be more efficacious for your condition than current treatments."). Appeals to self-interest usually do not constrain voluntary choice and, if accurate in their claims, are not otherwise problematic. A second variant of persuasion, which may be more problematic, is the use of pressure (analogous to what Faden and Beauchamp refer to as "psychological manipulation").[56] Drawing again from the *Oxford English Dictionary*, to apply pressure is "to urge or press strongly . . . ; to apply influence or psychological force." In the context of the decision to enroll in a trial, "pressure" means the application of psychological influence over time, within a relationship, in an attempt to influence a person's decision. Not all kinds of pressure negate the voluntariness of consent, though they may be more likely to do so than offers.

Like an offer, pressure can be thought of as undue influence if it is illegitimate and causally related to the decision. Pressure can be interpersonal (for example, a physician repeatedly urging a patient to sign up for a study in which the patient clearly does not want to participate[57]) or organizational (for example, a hospital defining expectations that patients will participate in research). It can emanate from within or outside the health care system. The closer the relationship between a person and a potential subject, and the more dependent the potential subject is on that person, the more likely pressure is to be effective.

Pressure is probably the most common behavior that constrains the voluntariness of decision-making in research. The following scenario from our research demonstrated the complexity of determining the effects of pressure: when a thirty-six-year-old man's boss suggested that he participate in a treatment study for his substance abuse, the subject felt pressured into enrolling. He rated the pressure as moderately important (five on a scale of ten) and moderately unfair (also five on a scale of ten). But he admitted that he needed help for his addiction, saying that half of his motivation was internal and only half was to please his boss. He also described himself as extremely pleased to be in the study.

Pressure can also be exerted in the opposite direction—that is, to discourage potential subjects from enrolling in research. For example, a thirty-seven-year-old woman who was enrolled in a drug abuse treatment study broke into tears while describing how her Alcoholics Anonymous sponsor had pressured her not to enroll, saying that it was not the kind of help she needed. The subject characterized the pressure as "wrong, unfair, close-minded, and stupid," but reported that in the end it did not affect her decision, which she believed she had made in a completely voluntary fashion.

An assessment of voluntariness might begin with a general inquiry into the motivations for a person's decision. The evaluator will want to pay particular attention to external and intentional influences that are most likely to impair the voluntariness of consent.

Parsons' final category of influence involves the application of force. In the doctor-patient relationship, force may be exerted through nonconsensual research participation—that is, enrolling a person in research without that person's consent—including surreptitious involvement (such as administering a study medication in food without the person's knowledge) or threats (such as telling a very ill patient that he or she will be discharged from the hospital unless he or she consents to participate in the study). Threats are declarations of intent to take action detrimental to another, contingent on that person's failure to behave in the manner desired by the individual or entity making the threat.

Nonconsensual research involvement may be *non*voluntary, but is not necessarily *in*voluntary (as defined above) if the patient is not competent

to make a decision, since such interventions may reflect legitimate choices made by appropriate surrogates. As with pressure, threats can come from clinicians, researchers, or from others who are significant to potential subjects. When used by clinicians or researchers to induce participation, threats are generally viewed as illegitimate. However, the same may not be true of threats made by other people in subjects' lives. A family member, for example, may have the right to make certain demands on a patient that a medical professional or researcher could not. The legitimacy of those threats can often be difficult to determine. For example, a substance abuse researcher reported that the family of one of his subjects told him that if he didn't participate in the study—which provided free treatment for addiction—then he couldn't live at home anymore. Their intent was to get him into treatment for his addiction in an available and affordable program. The subject was allowed to enroll in the research project.

A final component of this conceptualization of voluntariness is the recognition that constraints on decision-making can be either actual or perceived. Actual offers, pressure, or threats reflect the behavior of other people who are trying to affect the subject's decision. Previous studies of limits to voluntariness in the context of psychiatric hospitalization, however, have suggested that there is often a marked difference between the behaviors of others and a subject's perception of those behaviors.[58] Hence, both actual and perceived constraints are relevant. For example, a threat may be made in an attempt to coerce someone to perform an action—like join a research project—but the subject of the threat may not perceive herself as experiencing coercion, perhaps because she does not believe that the threat will be carried out. Conversely, a person may experience pressure when no pressure has been applied. For example, a person may believe that his physician will be angry with him for failing to enter a research project, even though the physician is actually indifferent to whether he enters the project. Although perceived constraint in the absence of intentional behavior may not render a choice legally involuntary (based as it is on the subject's own misperception), it may still be problematic from an ethical perspective, since the subject will be making a decision that cannot be said to reflect an informed choice. Thus, investigators may want to monitor for and correct such misperceptions prior to obtaining consent.

A Research Agenda on Voluntariness

A prerequisite for further research on voluntariness is to develop reliable and valid methods of assessing when constraints on voluntariness are present. That will require, in turn, a complete understanding of the nature of such constraints—including a method to detect their presence and, if necessary, to measure them quantitatively—and ways to put the resulting knowledge into practice. Given the potentially different implications of actual and perceived coercion and undue influence, developing ways of assessing both would be helpful.

Reliable assessment techniques would also open the door to studies of the epidemiology of constraints on voluntariness. In what types of studies, with which kinds of people, suffering from what categories of disorders are problems with voluntariness most likely to arise? How well does the reality of voluntariness match the assumptions found in the bioethics literature and the underlying regulation of researchers' practices? Is lack of voluntariness more of a problem in "total" institutions, such as prisons? Is it more likely to manifest in certain groups of vulnerable people, such as children, pregnant women, drug abusers, subjects recruited by their own physicians, people with mental disabilities, and people who are educationally and economically disadvantaged, particularly those without other access to medical care? To what extent and at what point do incentives have the feared effects on subjects' choices?

As answers to these questions begin to be available—and assuming that problematic areas of activity can be identified—a new set of issues with regard to preventing actual and perceived threats to voluntariness can be explored. What kind of education may be helpful for investigators and their staff? Which of the regulatory options available to IRBs (like caps on incentives or the use of consent monitors) are likely to be effective, and which are most cost-effective, taking into account the impact on the research projects themselves? To the extent that subjects may misinterpret clinicians' or researchers' behavior as constituting pressure or threats, what interventions may be helpful in clarifying the situation?

Assessing Voluntariness in the Research Setting

Like decisional competence, the voluntariness of decisions—including decisions to consent to research—is presumed by law unless evidence is presented that it has been illegitimately constrained. When questions arise about constraints on a subject's voluntariness, investigators may be at a loss to know how to structure their assessment. The most widely used instrument to measure patients' perceptions of coercion is the MacArthur Perceived Coercion Scale (PCS), a brief, five-item questionnaire. Even though the PCS was originally developed and tested in the context of consent to psychiatric hospitalization, a slightly modified version of this questionnaire may be helpful to uncover the extent to which subjects believe that their decisions are not their own,[59] and our experience suggests that this modified version can also be useful in research consent settings. But the PCS is not designed to probe the nature of the influences on respondents' decisions

or their legitimacy, and at the moment there is no validated assessment tool to assist in the process.

The conceptualization of voluntariness offered above may be helpful here. An assessment of voluntariness might begin with a general inquiry into the motivations for a person's decision about enrolling in research—with questions such as, "What made you decide to participate in the research project?" From the list of motives that most people will offer, the evaluator will want to pay particular attention to external and intentional influences that are most likely to impair the voluntariness of consent. Having identified these, the next step will be to assess their legitimacy. As noted above, pressure and threats by health care professionals will generally be problematic, but the same is not true for all people in the potential subject's life. However, not all pressure or threats from family members or friends are necessarily legitimate. For example, a threat to withhold the patient's Social Security disability check unless she agrees to enter a study is clearly unacceptable. Because of this, the nature of these actions must be carefully explored. Finally, the assessor will want to determine the extent to which they may have affected the ultimate decision of the subject.

As the examples above show, voluntariness occurs along a spectrum. Since subjects more often than not offer multiple reasons for enrollment, drawing a line between voluntary and involuntary actions is often not easy. Part of the challenge involves ascertaining the extent to which subjects' decisions were affected by offers, pressure, or threats. Additional dilemmas stem from the need to determine the legitimacy of those behaviors. We should keep in mind that our legal system presumes voluntariness of choice, and that this presumption should be overturned only in cases in which the four criteria for rendering decisions involuntary are clearly met.

Sometimes subjects may perceive themselves to be pressured or threatened when, in fact, they are not. Patients, for example, may believe that physicians will dislike them and be less attentive if they reject proffered study participation, or that they will be discharged from their physicians' care altogether. Clarifying the situation may free patients to make truly voluntary decisions. If illegitimate pressure is really present or threats really have been made, it may be necessary to seek administrative interventions. Intrafamilial conflict over research choices may be resolved by bringing in key family members for a group meeting with the person and responsible researchers, at which issues can be explored and appropriate parameters outlined for family members' involvement.

In practice, research settings generally deal with the assessment of potential threats to voluntariness on a prospective basis, as specified by the federal regulations. As noted above, IRBs are encouraged to consider requiring special protections for groups whose decisions might be rendered involuntary by offers, pressure, or threats.[60] This prospective regulation of the consent process, in contrast to what transpires in the ordinary clinical setting, is based on the assumption that whereas medical treatment is intended to promote the patient's best interests, research is designed primarily to produce generalizable data, and the likelihood that subjects will benefit is highly variable. Among other possible approaches, when subjects are believed vulnerable to impaired voluntariness, IRBs may appoint "consent monitors" to observe the consent process and to determine that subjects are giving voluntary consent.[61] To our knowledge, the utility of such monitors has not yet been studied. Other approaches to protecting voluntariness should be explored as well.

Our conceptualization is drawn from the approach to voluntariness taken by the legal doctrine of informed consent, with its focus on assessing objective behaviors of researchers and their impact on subjects' decisions. Whether consent is voluntary, therefore, depends on the extent to which subjects are actually exposed to external, intentional, and illegitimate influences that causally impact their decisions. The regulatory structure surrounding human subjects research, and the reality that challenges to the validity of consent will ultimately be resolved in the courts, combine to support this approach.

But voluntary decisions are not necessarily optimal ones, since they may still be uninformed or unwise, or made in the mistaken belief that external constraints exist. Hence, exploration of ways to maximize subjects' informed participation in decisions about research remains important. However, a clearer conceptualization of voluntariness, rooted in the law of informed consent, should help to advance scholarship, research, and practice on those aspects of researchers' behavior that may compromise voluntary consent in research settings or be perceived by subjects as having done so.

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