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The Ethics of Withdrawal from Study Participation

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Abstract

We investigated whether consent forms adhere to Federal Common Rule regulations pertaining to withdrawal from research, described the language of withdrawal provisions, and assessed differences in studies by withdrawal provisions. A random sample of 114 consent forms from a Midwestern, academic medical center were examined for descriptive content of withdrawal parameters stated within consent forms. All consent forms included the required statement about withdrawal pursuant to the CFR regulations [21 CFR §50.25(a)(8)], and all adhered to regulation [21 CFR §50.25(b)(4)] by including a statement that withdrawal will have no affect on care provided. Of 114 studies, thirty (26%) studies explicitly requested subjects/participants to engage in a further behavior before withdrawing from the study. Safety was mentioned in only 4 (13%) instances as the reason for an additional visit or test. None of the consent forms provided information about the consequences to the subject's health or well being by withdrawing from study participation. Consent forms generally conform to current regulations. Future research should examine subjects' experiences of withdrawing from research in order to help clinical investigators and Institutional Review Boards assess the extent to which consent forms indicate barriers to withdrawal and for compliance with Federal Common Rule regulations.

Keywords

consent form; withdrawal; policy; clinical research; Federal Common Rule; content analysis; voluntariness; undue influence

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While considerable attention has been directed toward the informed consent process and ethical recruitment of human subjects into research protocols, relatively less attention has focused on possible ethical concerns pertaining to the withdrawal process and dis-enrollment of participants once recruited. While there are eight main and six additional Federal requirements for informed consent to enter subjects/participants into research studies, two of them pertain to leaving a study. The U.S. Code of Federal Regulations (CFR) regarding voluntary withdrawal from research clearly requires communicating terms of withdrawal and that requests for withdrawal will be granted without repercussions to the participant. The Federal Common Rule requires informed consent documents to include information on withdrawal from research participation: "…the subject may discontinue participation at

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any time without penalty or loss of benefits to which the subject is otherwise entitled" [45 CFR §46.116(a)(8)]. Additionally, the CFR stipulates that the consent document must address, "when appropriate": "The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject" [45 CFR §46.116(b)(4)]. The U.S. Food and Drug Administration (FDA) also maintains identical respective regulations [21 CFR §50.25(a)(8)] and [21 CFR §50.25(b)(4)], although most research conducted under FDA regulations is supported by the pharmaceutical industry. Such regulations make clear that subjects/participants are free to withdraw from study participation at any time. However, the point at which withdrawal procedures become too cumbersome to subjects and are perceived as undue influences to remain in the study remains to be determined.

Little is known about whether consent forms actually adhere to these two Common Rule regulations. Additionally, the kinds of procedures requested and/or required of subjects to withdraw from research have not been examined. The withdrawal section on informed consent forms can include additional stipulations necessary for withdrawal suggesting that subjects cannot simply leave a study at any time. Ascertaining whether consent forms include provisions regarding withdrawal and/or whether such provisions include additional stipulations necessary for withdrawal is important because subjects/participants may perceive them as simply persuasive tactics or as undue influences, and possibly even coercion, to continue to participate in a research study, undergo burdens, and be exposed to unwanted health risks. But the distinction between how subjects perceive and/or experience these concepts is unclear and should be clarified.

Persuasion occurs when "a person must be convinced to believe in something through the merit of reasons advanced by another person" (Beauchamp and Childress 1986:164). Persuasion is an ethically acceptable and common practice among health care professionals in the context of treatment in an effort to ensure that patients undertake the most healthful course of action (e.g., Scales and Miller, 2003). However, there is controversy over the role of persuasion to recruit or retain subjects within clinical research. It is unethical to undermine voluntary consent, but when research is therapeutic and no other options are available off-study, the use of persuasion may be justified (Nelson and Merz, 2002).

Undue influence "occurs through an offer of an excessive, unwanted, inappropriate or improper reward or other overture in order to obtain compliance" (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Inducements may become undue influences if the subject is especially vulnerable. (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). The Belmont Report makes clear that:

"Unjustifiable pressures usually occur when persons in positions of authority or commanding influence – especially where possible sanctions are involved – urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services

to which an individual would otherwise be entitled" (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979).

In contrast, coercion occurs when "the choice a research participant makes is constrained by another person, such that the research participant has no alternative but to do what the other person wants him or her to do" (Agrawal, 2003:S27). In the context of withdrawing from clinical research, when investigators request or require that subjects undergo additional actions before withdrawing from study participation, subjects may perceive coercion because they may prefer to leave a study but feel that they have no choice but to remain, or the incentive to stay is too high, or the effort to leave is too high.

Certainly, there is a subjective component to assessments of undue influence, and as the Belmont Report states, there is no clear distinction between persuasion and undue influence. How subjects perceive withdrawal stipulations likely depends on various strategies employed by clinical investigators that could potentially make subjects reconsider or feel uneasy about leaving. These strategies may be induced in terms of financial factors or time and effort, and less obvious psychological strategies pertaining to subjects' sense of obligations to clinical investigators/physicians. The uncertainty over how to interpret withdrawal stipulations in light of concerns over persuasion, undue influence, and coercion warrants further ethical attention in order to make further distinctions and protect human research subjects.

What remains to be determined is the point at which withdrawal stipulations bear undue influence or become potentially coercive to the subject/participant to stay in the study. While this information can only be obtained through interviews with research subjects (which is beyond the scope of this paper), it is worth pointing out the continuum by which withdrawal stipulations may generate concerns about persuasion, undue influences, or coercion based on an increased level of effort expected of subjects for withdrawal. Certainly, the most expedient option is to require (or request) subjects/participants to do nothing other than state their intention in order to withdraw from a study. While this option confers the greatest freedom to subjects/participants, it is associated with other problems, which will be examined below. A slightly more cumbersome withdrawal procedure would be to ask patients their reasons for deciding to withdraw from research. An even more demanding withdrawal procedure would require participants to engage in further behavior and extensive withdrawal procedures, such as additional tests and visits. These options span a continuum along which Principal Investigators (PIs) and their Clinical Investigator (CI) collaborators may request or require additional behaviors of study subjects/participants for which their ethical soundness must be examined.

The occurrence of additional withdrawal stipulations in consent forms may very well be related to different study characteristics. In particular, four study characteristics -- phase of clinical trial, whether the research was therapeutic, study sponsorship, and IRB review level -- should be considered for the following reasons. First, phase of clinical trial is relevant because it may very well be that the risk-benefit ratio differs by trial phase thus requiring different levels of attention to patient monitoring. Second, the therapeutic status is important to consider because studies pose different levels of risk depending on their therapeutic

status, which accordingly may require different levels of patient oversight. For example, therapeutic studies generally present higher risks to subjects than nontherapeutic studies. Third, study sponsorship is relevant to how consent forms are written because sponsors vary in the level of oversight of study participants and in the review of consent forms. Sponsors with more rigorous data collection requirements will likely have greater subject oversight mechanisms. For example, the NIH requires considerable oversight of study participants. Conversely, it may be that other funding sources require less attention to addressing issues of withdrawal and subject oversight. Lastly, the level of IRB review is important because it reflects differences in the level of study oversight. For example, studies requiring full IRB review require greater clinical and ethical oversight given the greater potential for harm to subjects. PIs of protocols presenting greater risks to subjects may desire greater monitoring of such patients by including additional withdrawal stipulations that request subjects to notify them or undergo further tests.

Ensuring that subjects/participants can voluntarily withdraw from study participation without consequences is a basic tenet of patient self-determination. Reviewing consent forms for withdrawal provisions is a good way to a) raise awareness of both the variation in withdrawal procedures on consent forms, and b) begin an assessment of the ethical parameters of withdrawal. This study set out to determine whether barriers to withdrawing from study participation exist on consent forms. The study aims were designed to:

1. Measure the frequency in which consent forms adhered to the Common Rule regulations;
2. Assess whether certain study characteristics (phase of clinical trial, whether the study proposed to do therapeutic research, study sponsorship, and type of IRB review) are related to the presence of additional withdrawal stipulations;
3. Measure the frequency in which consent forms explain why withdrawal procedures are necessary for the subject's welfare; and
4. Examine the language by which withdrawal procedures are framed to explore whether messages of persuasion or undue influence might be perceived.

Our hypotheses pertain to study aim #2. It is hypothesized that phase I trials would have greater details pertaining to withdrawal stipulations than phase II or phase III trials. It is hypothesized that therapeutic studies would have greater specificity in detail regarding withdrawal stipulations than nontherapeutic studies. It is also hypothesized that NIH-sponsored studies would have the greatest level of details regarding withdrawal stipulations than protocols with other funding sources, and that studies requiring full IRB review would include more additional withdrawal stipulations than studies requiring expedited review.

This paper presents findings on withdrawal provisions as noted on consent forms and discusses the ethical implications of additional stipulations to withdrawal from study participation beyond CFR guidelines. Discussion focuses on the potential ethical reasons for requiring subjects to remain in the study beyond their preference.

METHODS

To investigate adherence to Federal Regulations pertaining to withdrawal, and procedures for withdrawal from study participation, we conducted a content analysis of withdrawal parameters as stated in a sample of consent forms from all IRB-approved active studies approved by one Midwestern, academic hospital's Institutional Review Board (IRB) between 1992 and November, 2002. To be clear, withdrawal parameters stated on the consent form boiler plate were not included in this analysis so as to highlight the practices of individual investigators rather than one institution's policy. A total of 477 protocols involving human subjects research were active and eligible for inclusion. Retrospective chart review studies were excluded from analysis because there is a waiver of informed consent, and thus no document to review. This resulted in a total of 342 protocols eligible for analysis. A random sample of 33% resulted in a sample of 114 consent forms included for analysis. The withdrawal section of consent forms was assessed for the existence of statements of omission and commission pertaining to specific circumstances under which withdrawal occurs. Most, but not all, consent forms reviewed were for clinical studies, with physicians serving as the principal investigator. While most protocols included adult participants, some protocols included children or both adults and children. Insufficient information about subject eligibility on some consent forms prevented us from definitively ascertaining subject age status and undertaking an analysis of this variable. IRB approval for this research was granted by Loyola University Medical Center.

Independent variables pertaining to study characteristics included: phase of clinical trial, whether the study proposed to do therapeutic research (e.g., offering direct benefit to the subject/patient), study sponsorship (e.g., no funding, pharmaceutical company funded, or federally funded e.g., by a National Cancer Institute cancer clinical trials cooperative group), and type of IRB review (e.g., expedited review, full board review). We defined therapeutic research as studies in which participants may be expected to receive direct benefit from their involvement in the study. An example of therapeutic research is a phase III clinical trial designed to determine the effectiveness of an investigational drug compared to an FDA-approved drug for metastatic non-small cell lung cancer. Conversely, we defined nontherapeutic research as a study that is designed to obtain further knowledge but is not expected to be of direct benefit to the participant(s). An example of a nontherapeutic study is a study designed to determine the toxicity levels of four different doses of an investigational drug for possible use to decrease blood clots in bypass grafts. We used the stated study benefits section within consent forms at face value regarding the protocol's therapeutic status.

All study characteristics and statements conveying additional stipulations to withdrawal beyond that required by the Common Rule regulations were entered verbatim into the statistical database, SPSS 12.0 (SPSS, Inc., Chicago, IL). Analysis entailed descriptive statistics, and univariate analysis involving testing differences in proportions using Pearson's Chi-square test or Fisher's exact test if expected frequencies were less than five. Logistic regression (backwards) was used to examine multivariate relationships between study characteristics and the dependent variables of sufficient sample size in the distribution of scores. These dependent variables included notify the PI, and a combination of three

variables: notify the PI, return for another visit, and return for further testing, called “All Stipulations Combined.” All tests were two-tailed and $p < 0.05$ was considered statistically significant.

A content analysis was conducted for each consent form by systematically searching for themes and repetitions pertaining to additional steps to withdraw from study participation beyond those required by the Common Rule that emerged from the data (Luborsky, 1994; Huberman and Miles, 1994). Themes were developed by grouping coded segments into larger domains, reviewing the categorization schema for appropriate thematic fit, and then adjusting and reviewing the schema again until categorization and interpretation were sound. Two research assistants and one investigator (EJG) reviewed consent forms, and the investigators examined consistencies in the results.

RESULTS

Of the 114 consent forms examined, exactly half were for studies conducting therapeutic research and had no external sponsorship, and over three-quarters were phase I clinical trials and were fully board reviewed (see Table 1). The studies varied in clinical conditions researched: the most common conditions were cancer, cardiovascular, and infectious diseases; the least commonly studied conditions included dermatology, orthopedics, and renal.

Adherence to Federal Regulations

All consent forms included the required statement about withdrawal pursuant to the CFR regulations [45 CFR §46.116(a)(8)] by including a statement to the effect that withdrawal will have no impact on the care to which individuals are otherwise entitled. We were unable to fully ascertain whether consent forms adhered to [45 CFR §46.116(b)(4)] as only the PIs of the respective studies are fully capable of ascertaining this need. Despite consent forms including a statement that withdrawal will have no affect on care provided, none of them provided any information about the consequences to the patient’s health or well being from study withdrawal. One consent form tangentially addressed this point by providing a statement that subjects/patients will be informed of medical issues when they withdraw. No consent forms actually listed potential risks or stated that there are no known risks to subjects/patients for withdrawing from study participation. In both of these regards, the consent forms reflect PIs’ partial noncompliance with regulation [45 CFR §46.116(b)(4)] in that full disclosure of the consequences of withdrawal have not been made. None of the 114 consent forms in the entire sample provided explicit directions or steps to patients on how to withdraw from a study which reflects nonadherence with regulation [45 CFR §46.116(b)(4)]. Even for those protocols requesting additional procedures, no details were provided on how to carry them out beyond contacting their physician in a subset of studies.

Withdrawal Stipulations

Of 114 studies, thirty (26%) studies had explicitly requested subjects/participants to engage in a further behavior before withdrawing from the study. Of these thirty studies: 21 (18.4%) requested subjects to notify the Clinical Investigator (CI) of their desire to leave the study; 8

(7.0%) requested subjects to return for another visit for a variety of reasons and procedures; and 6 (5.3%) requested subjects to return to the clinic for further testing. The requests for subjects to return for another visit and to return for further testing are similar in that they are both forms of monitoring subjects/patients through the collection of additional information. However, the former set of requests seeks to collect patient self-disclosed information, while the latter set of requests collects clinical information through physically invasive tests or procedures. Two of these withdrawal stipulations directly required subjects to either notify the CI or undergo another test. Five protocols specifically noted two or more stipulations for withdrawing. Of these five studies, three requested subjects to both notify the CI and undergo further tests; and two studies requested subjects to both undergo another visit and further tests. Table 1 presents the characteristics of these three groups of studies and the total sample in terms of study characteristics.

Study Characteristics Related to Additional Withdrawal Stipulations

Significant relationships were found when analyzing the set of three withdrawal stipulations together, and within the subset of consent forms requesting subjects to notify the PI, as Table 1 shows. With regard to analyses of the set of withdrawal stipulations combined, we found that additional withdrawal stipulations were significantly more likely to be found in consent forms for phase I clinical trials than consent forms for phase II or phase III clinical trials (Chi-square = 12.25; $p = 0.002$). Studies proposing therapeutic interventions were significantly more likely to be found among study consent forms with withdrawal stipulations than in study consent forms without withdrawal stipulations (Chi-square = 11.58; $p = 0.001$). Additional withdrawal stipulations were significantly more likely to be found in federally funded studies than in studies with other or no funding sources (Chi-square = 26.23, $p < 0.0005$). When these parameters were combined in a multivariate analysis, study sponsorship was the only variable significantly associated with the presence of additional withdrawal stipulations.

Explanation for Additional Withdrawal Procedures

Ten (33%) of the thirty consent forms provided information on why additional withdrawal procedures are necessary. Four of these consent forms state that the withdrawal request enables the disclosure of additional information to the subject, which is intended to encourage subjects to remain in the study. In four others, the reason briefly provided is for safety purposes. Two consent forms state that the request will enable further scientific study. The following discussion reveals how the explanations are presented in the context of consent forms.

Language of Withdrawal Stipulations

The language in which these kinds of barriers are described can bear upon subjects' decisions about participating in research. Specifically, how the statements regarding withdrawal are framed can convey information as to how much the research team expects or desires the subject to heed the request.

Notify the Doctor—The most common way in which consent forms requested the subject to notify their doctor was phrased as follows: "However, if you decide to stop participating

in the study, we encourage you to talk to your doctor first." By stating 'we encourage you,' the consent form conveys the sense that the PI is making a request, which the subject/patient may voluntarily decline. A closer look at the structure of this request reveals a tacit process that researchers seem to expect study participants to follow should they consider withdrawing from the study: subjects should make a decision, then notify the physician, and thereafter stop involvement in the study. This framework can be interpreted in two possible ways. On one hand, it may be the case that the PI is concerned for the subject/patient and wants him or her to be fully informed prior to withdrawal. Alternatively, the PI may have an agenda to retain subjects in a study even after subjects express a desire to leave. This agenda was explicitly expressed on four (3.5%) consent forms, as in the following request: "However, if you decide to stop participating in the study we encourage you to talk to your doctor first. We will tell you about important new information that may affect your health, welfare, or willingness to stay in the study." The way this request is worded can convey the sense that the PI is either trying to inform the patient about risks, or more cynically, alarm subjects/patients into giving them more data. These four were the only consent forms that provided an explicit rationale for why subjects should notify their doctor.

There were other ways in which the request to notify the CI actually seemed less voluntary, such as when "we recommend" was used. Further, using the directives, "please inform," "you must inform," and "please let the research staff know," directly *requires* or comes close to requiring subjects/patients to engage in further study behavior before disengaging from the study.

Additional Visit—Consent forms described the request for the return visit to the clinic in the following ways:

"If you should decide to discontinue receiving study drug, you will be asked to come to the clinic for a discontinuation visit." (n=3)

"If you withdraw after receiving the investigation product, we strongly recommend that you continue to see the doctor to determine the safety of the study procedures." (n=1)

"If you should decide to discontinue receiving study drug, you will be asked to come to the clinic for a final visit (which will be similar to your regular study visits) or telephone interview to complete the questionnaire about the safety information of the study drug between 35-49 days after your surgery." (n=2)

"If you leave the study for any reason, you must return all unused test/articles. You may be asked questions about your experiences." (n=2)

The main reason for asking subjects to return for a visit, as these quotes illustrate, is to collect additional data, through questionnaires or interviews, about the subjects' experiences of participating in the study or safety issues. Only in three instances was safety identified as the reason for the additional visit. Presumably, subjects would visit the clinic at the time they return study items, as in the last quote. All of these withdrawal stipulations request that subjects undertake additional steps after their stated desire to withdraw.

Additional Clinical Testing—Consent forms requested that subjects return to the clinic for further testing as the following shows. The issue of safety versus scientific study is an important one embedded in the quotes appearing in the withdrawal section of the consent forms.

"You may also be asked to undergo whatever lab tests and physical exams deemed necessary." (n=2)

"Additional samples of blood and bone marrow will be taken for purposes of scientific study." (n=1)

"Depending on the results of these tests we may ask that you donate an additional four teaspoons of blood for further studies." (n=1)

"We will ask that you have final blood tests and clinical assessment." (n=1)

"You will be asked to complete the following tests and procedures for your safety: a physical exam, a collection of blood and urine samples for lab tests, measurement of your blood pressure and pulse rate; and review changes in your health and medicines." (n=1)

Two of these requests were made for the purpose of advancing the scientific study. Safety was identified only once (in the last example) as the purpose of requesting the additional tests after subjects withdraw from the study. However, little beyond identifying this purpose was provided. That is, the consent form contained no information about how risky or dangerous it is to subjects should they choose to forego such tests. Again, these withdrawal stipulations request that subjects undertake additional steps after their stated desire to withdraw.

DISCUSSION

To our knowledge, this is the first study to empirically examine whether consent forms from IRB-approved studies adhere to human subjects protections regarding withdrawal from study participation, and examine additional steps to withdraw from study participation beyond those required by the Federal Regulations.

Adherence to Regulations

All consent forms adhered to [45 CFR §46.116(a)(8)] and part of [45 CFR §46.116(b)(4)], indicating that PIs are in full compliance in reference to regulations already stated in the CFR. However, no consent forms adhered to the part of [45 CFR §46.116(b)(4)] pertaining to stating the consequences of withdrawal on patient health and well-being. It may very well be the case that the PIs of the consent forms thought it was not appropriate to include the consequences in the consent forms, or that the PIs simply did not view this Federal regulation as being relevant in their research protocol. That is, PIs may experience difficulty interpreting the regulation phrase, "when appropriate," that precedes the required statements regarding the consequences of withdrawal and procedures for orderly termination. It may also be that there is concern on the part of PIs that extensive articulation of withdrawal

statements may be construed as a factor contributing to deterring recruitment into research in the first place.

Without Federal regulations clarifying what “when appropriate” means, determinations are left up to the PI. Accordingly, consent forms likely vary in their adherence to this regulation which may infringe on study participants’ freedom. PIs must ensure that both regulations [45 CFR 46.116(a)(8)] and [45 CFR 46.116(a)(4)] are followed in order to sufficiently protect human subjects.

Yet this does not necessarily mean that all consent forms should state the consequences of withdrawal as this will likely depend on the type of study. For instance, based in part on concerns about safety discussed below, we propose that therapeutic studies, especially those in which subjects are more likely to be vulnerable because they are at the end of life and/or have no other available treatment options, e.g., phase I or phase II studies, as well as long-term studies aimed at the disease as opposed to studies of short, surgical procedures, would merit the inclusion of consequences. This is a matter of further discussion among ethicists, PIs, and IRB members. There may be, however, other kinds of justifications, besides safety, that have yet to be identified which justify the inclusion of the consequences of withdrawal. Nonetheless, the nonadherence to this Federal Regulation is sufficient to generate concern over the ethical provision of informed consent for subjects/patients participating in (mostly clinical) research. The absence of statements regarding the consequences of withdrawal in consent forms suggests the IRB need for further guidance on interpreting withdrawal stipulations.

Withdrawal Stipulations

In over a quarter of all studies examined, consent forms stated a request for subjects/patients to either notify their doctor and/or undergo an additional visit and/or clinical test. The occurrences of these withdrawal requests on consent forms may be related to variation in how PIs and IRBs interpret Common Rule regulations (see Vick et al., 2005; Silverman et al., 2001; Rogers et al., 1999). For example, other research examining ‘benefits’ statements in consent forms for participating in genetic research has shown that ‘benefits’ are construed in myriad ways (Henderson and King, 2001; Churchill et al., 1998). Such inconsistency is problematic for patients/subjects as it may undermine their ability to be appropriately informed about studies and make decisions about participation (King et al., 2005). Since variation also exists in the consent form section on study withdrawal, then concerns similarly apply regarding the potential to undermine subjects’ decisions about participation and about ending involvement in a study.

In univariate analysis we found that withdrawal stipulations were more likely to be found in phase I studies compared to phase II or III trials, therapeutic research, and federally funded studies. It may be the case that PIs include withdrawal stipulations in consent forms for these three types of studies as a way to bolster patient monitoring since such studies pose greater risks. Greater efforts to monitor subjects make sense given the context of increasing concerns over scientific integrity (Shamoo and Dunigan, 2000; Macrina, 2000) and clinical investigator vigilance in adverse event reporting (Bennett et al., 2005), which is especially rigorous in federally funded studies. In multivariate analysis, however, we

found that only study sponsorship was related to the occurrence of additional withdrawal stipulations. Upon further analysis, associations among some parameters (e.g., therapeutic status and source of funding) (within n=30 and n=114) are significant and may represent some other underlying concept that results in greater details in consent form development pertaining to withdrawal stipulations. Upon further examination of associations among these variables, study sponsorship tended to be associated with phase III and therapeutic studies.

The presence of additional withdrawal stipulations in these consent forms expresses the PI's expectation that subjects should remain in the study beyond their stated wishes to leave. This expectation runs contrary to the assumption that subjects' declarations of their wish to withdraw should go into effect at that very point in time. Indeed, the Federal Regulations make clear that individuals may withdraw at any time. As long as subjects are informed about the potential risks of withdrawal, it is essential that subjects be enabled to withdraw at any time. Yet, given that the withdrawal stipulations were written without sufficient information in consent forms, this ethical requirement may present a risk to subjects and therefore merits further analysis, which we provide below.

The fact that most consent forms with additional withdrawal stipulations failed to provide explicit explanations for why the request for further action by subjects/patients is necessary is ethically troublesome. This is because federal regulations [45 CFR §46.116(b)(4)] call for a description of the consequences of subject withdrawal which would essentially subsume an explanation for why such requests are necessary. In order for withdrawal requests to become ethically justified, an explicit explanation is necessary. We found that the only explanations provided for withdrawal requests in consent forms were to disclose further information with the intention of either informing subjects about their health and welfare or encouraging subjects to remain in studies, for safety purposes, or for the purpose of advancing the scientific study. We argue that such requests made solely for the purpose of encouraging subjects to remain in studies and/or for advancing the scientific study are unethical because they undermine subject autonomy and there is no benefit to subjects of continued participation after subjects have stated their desire to withdraw. Protecting the rights of human subjects involved in research and who desire to leave research must have priority over the advancement of scientific pursuit, as Hans Jonas has so well expressed decades ago (Jonas, 1969).

The key question the study results raise is whether additional withdrawal stipulations are ever ethically justified. Arguments for or against the use of withdrawal stipulations depend largely on the type of study and explanations justifying the use of withdrawal requests, and can be understood in terms of patient autonomy, patient safety, and subject commitment to research.

Arguments in favor of withdrawal stipulations—The request, (and not requirement), for further tests and clinic visits may be justified on the grounds of respecting patient autonomy. A request to notify the doctor, undergo another visit or medical test can be construed as simply a request which the subject/patient is free to decline. As autonomous agents, subjects/patients can choose whether to meet the PI's request. Certainly, drop out

rates of clinical research – commonly reported to be 9% and even as high as 20% (Lewis, 1984) – demonstrate clear evidence that patients exert their agency to do as they will.

Withdrawal parameters requesting subjects to return for further testing can be justified on the grounds of protecting subject/patient safety. As Levine (1986) has pointed out, there can be serious hazards to subjects' health upon withdrawing from drug therapy research. In such cases, the PI is interested in establishing whether the study drug has harmed the subject; further tests may help to protect subjects from further harm. He therefore suggests that subjects be informed of the risks of withdrawing from research (Levine, 1986). Without providing information about the risks and benefits of undergoing further tests, the current policies do not sufficiently protect subjects or inform them about the procedure(s) for withdrawing from a study.

The concern over ensuring subject/patient safety may ethically justify the request for further testing for therapeutic research but not for nontherapeutic research, because the former research tends to pose higher risks to subjects than the latter. Moreover, therapeutic research involving subject follow-up after study completion to ensure that medication is safely tapered, as in the case of methadone studies, for example, does not necessarily constitute a barrier to withdrawal since participation in research has already ended. Depending on how withdrawal stipulations for additional behaviors like returning to the clinic for another visit are construed on consent forms -- as part of the research or treatment – such withdrawal stipulations may not necessarily constitute barriers to withdrawal. Nevertheless, how withdrawal stipulations are construed in the view of the PI must be stated on consent forms.

The use of persuasion to encourage subjects/patients to remain in a study -- as manifested through withdrawal stipulations -- may be considered ethical for therapeutic research for other reasons. When therapeutic research, e.g., phase III clinical trials (such as for children, see Kodish, 2005) offers the best treatment option for subjects/patients, then it may become incumbent upon the physician-investigator to encourage study participation. In contrast, encouraging subjects to remain in nontherapeutic research shifts the risk/benefit ratio to where the subjects' benefit can not justify the added stipulations for withdrawal.

Another way scholars may conceptualize the ethical merit of additional withdrawal stipulations is in terms of the moral obligation research participants have to researchers. It has been argued that once committed, subjects/participants have an ethical duty to participate and remain in research, particularly when research entails little or no risk (Edwards, 2005; Levine, 1986). The "promise" that some philosophers believe subjects putatively make to researchers in their 'service to the community' means that they promise to do all that is expected of them, even upon leaving a study (Jonas, 1969; Newton, 1984).

The request to notify the CI may very well be justified as an expression of commitment to the research. First, it is considerate of subjects to inform the CI when they change their mind about remaining in a study after having initially agreed to it. Second, the PI, especially in therapeutic studies, may wish to recommend treatment, make a referral, or ensure that the subject is clinically stable -- all of which serve to ensure continuity of care. Third, should

subjects simply walk away from a study without informing the CI and adverse events occur thereafter, lawsuits may arise. Formal protections and mechanisms may need to be set in place.

Arguments against withdrawal stipulations—There are two main arguments against the use of withdrawal requests in consent forms. These arguments are based on the premise that the investigator/subject relationship is ambiguous and fraught with power dynamics, and that the withdrawal stipulations themselves are ambiguous – both of which can exacerbate subjects' vulnerability which in turn, undermine their voluntariness.

The presence of withdrawal requests on consent forms may present a barrier to withdrawing from study participation. This is because in the context of human subjects research, power differentials remain a factor influencing subject/participant and researcher dynamics (Gailey, 1998; King et al., 1999). This is especially a concern in clinical research where the subject is also a patient of the PI or CI, and traditional power structures and trust continue to affect the subject/patient-physician/investigator relationship (Hougham et al., 2003; Nurgat et al., 2005). In the context of the doctor-patient relationship, patients may feel compelled to be polite and a "good patient" and therefore follow recommended directives (Ainsworth-Vaughn, 1998; Mishler, 1984; Brody, 1992). As a result, patients/subjects will do what a CI/physician asks of them, trusting that the requested act is worthwhile to do.

Another reason why withdrawal requests should not be made of subjects or at least be made with caution is because they are phrased in an ambiguous way making it difficult for subjects to determine whether they are necessary. Making requests of subjects/patients for additional visits or tests may appear as a form of a question, even though the request is not structured as one. One of the requests identified earlier serves as a good example of this point: "We will ask that you have final blood tests and clinical assessment." Even though the PI may be technically asking the subject/patient to do some thing, the structure of the sentence appears more so as a directive rather than as a question. That is, the distinction between requests and requirements may be perceived as equivalent depending on how these withdrawal stipulations are phrased. The presence of the request and the way it is stated on the consent form may serve to foster compliance with the physician/investigator's request thus undermining subjects'/patients' freedom to withdraw at any time.

Even if the withdrawal stipulations can be made based on safety considerations, there is no apparent ethical justification for notifying the CI, nor for undergoing another visit for the sake of completing research questionnaires. The Health Information Portability and Accountability Act of 1996 regulations can also be interpreted as presenting a barrier to withdrawal. Requiring subjects to sign and return a revocation form should they decide to withdraw and revoke their consent to have data collected on them may be perceived as a burden on the study participant to opt out of the study.

One might contend that the concern over the content of consent forms, as it pertains to additional withdrawal stipulations, is excessive. Granted, the consent form is only one part of the overall consent process (Lidz et al., 1988), thus, caution must be taken when interpreting the gravity of these written stipulations. One way to address this concern is

to consider, what degree of power to affect decisions regarding participation in research do consent forms really carry? There is certainly controversy over their value and use (Meisel and Kuczewski, 1996; Brody, 2001). Research has shown that cancer patients remain confused and have poor recall about the nature of studies or therapy after reading and signing consent forms (Graham 2003; Montgomery et al., 1999; Meade, 1999), and that consent forms play little role in consent decisions to enter research (Gotay, 2001; Jaffe et al. 2001; Schaeffer et al. 1996). However, the fact that cancer patients in one study were more likely to retain information regarding the right to withdraw from clinical trials than information about risks and alternative therapies immediately and six weeks after providing informed consent (Schaeffer et al. 1996) suggests that the right to withdraw remains as an important feature for subjects. Nonetheless, additional withdrawal stipulations come close to legally breaching or in few cases actually breach Federal regulations because they interfere with subjects' fully-informed ability to withdraw voluntarily at any time and for any reason. Research subjects should be fully informed not only of the right to withdraw voluntarily but also of the consequences of withdrawal. It is the lack of being fully informed that is subject to research subjects' interpretation and decision making about whether to remain in studies. This analysis suggests that the same level of risks and benefits of getting into a study should also be articulated in consent forms for getting out of a study.

Recommendations

IRBs should more rigorously evaluate consent forms for indications of barriers to withdrawal and for CFR compliance. Further, IRBs should evaluate consent forms to ensure that sufficient information is provided regarding: a) the rationale for undergoing more than minimal withdrawal procedures such as another visit or test or contacting the CI; b) potential risks to subjects who do not undergo these or other recommended further steps prior to withdrawal; and c) the procedures for safe withdrawal if safety is a concern.

Before submitting for IRB review consent forms that include recommendations for subjects to undergo further steps prior to withdrawal, PIs should assess whether their withdrawal procedures are legitimate, that is, for safety purposes or risk analyses, and should state the reasons for such procedures in withdrawal instructions. We recommend a broader way to frame the request to notify the CI on the consent form: "It would be helpful to us if we understand your reasons for leaving the study, but we do not want to make this burdensome on you. If you could, we would appreciate it if you could please respond to a couple brief questions." Granted, these additional sentences may increase the length of some already lengthy consent forms, an issue unto itself. Recommending additional steps for the purpose of subject retention and further data collection is not ethical. Instead, PIs can use several strategies known to successfully enhance subject retention rates (Keller et al., 2005; Bender et al., 2003).

Our study has limitations. First, since the study was conducted at a single institution, our findings may not be generalizable to other academic medical institutions. However, the institution is nationally renowned for its four major research institutes. Second, based on the consent form, it is unknown whether the PI was also a patient's physician for the studies examined herein, which is highly controversial (Kass, et al., 1996). Third, although the

concept of “therapeutic research” is controversial, our operational definitions were based on Federal definitions and what consent forms stated. We had to rely on information provided in the consent form related to benefit as a definition of therapeutic/nontherapeutic research. Another limitation is that our unit of analysis was study consent forms rather than individual subjects’ perceptions of undue influences in withdrawal parameters.

Further research is needed to investigate subjects’/patients’ experiences of withdrawing from study participation, the steps they took to do so, and whether they encountered or perceived barriers to withdrawing. Additionally, research should examine subjects’/patients’, CIs’, and IRB members’ respective assessments of persuasion, undue influence, or coercion regarding consent form stipulations to notify the PI, and undergo further tests or an another clinic visit for withdrawal from study participation. Future research should also investigate the point along the continuum at which investigators, through consent form stipulations, transition from persuasion to undue influence when subjects/participants chose to withdraw.

In sum, policy makers, research investigators, and bioethics scholars spend considerable efforts to obtain informed consent for subjects to enter into research studies. This study shows that we need to focus attention on rescinding informed consent, and possibly provide more rigorous guidelines regarding withdrawal from study participation. It is unknown how much requested effort to withdraw is appropriate. It is not clear that additional withdrawal stipulations represent persuasion or undue influences or that the additional effort associated with them is appropriate. The sense of what constitutes undue influences in withdrawal procedures is unknown and likely differs considerably among three players: research participants, PIs, and IRBs.

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TABLE 1

Characteristics of Consent Forms Presenting Barriers to Withdrawal[*]

	Notify the PI[‡] (n = 21) N(%)	Return for Another Visit (n = 8) N (%)	Return for Further Testing (n = 6) N (%)	All Stipulations Combined (n = 30) N (%)	No Barriers (n = 84) N (%)	Total Sample (n = 114) N (%)
Phase of clinical Trial[†]						
Phase I	11 (55)[//]	7 (88)	4 (67)	19 (63)[°]	77 (92)	96 (85)
Phase II	3 (15)	0	1 (17)	3 (10)	1 (1)	4 (4)
Phase III	6 (30)	1 (12)	1 (17)	7 (23)	6 (7)	13 (11)
Therapeutic research						
Yes	16 (76)[§]	6 (75)	5 (83)	23 (77)[°]	34 (40)	57 (50)
No	5 (24)	2 (25)	1 (17)	7 (23)	50 (60)	57 (50)
Study Sponsorship						
In house (no sponsor)	3 (14)[//]	0	1 (17)	3 (10)[//]	54 (64)	57 (50)
Company	5 (24)	7 (88)	3 (50)	13 (43)	13 (16)	26 (23)
Federal funding	13 (62)	1 (12)	2 (33)	14 (47)	17 (20)	31 (27)
IRB Review Level						
Full Board	20 (95)	7 (88)	6 (100)	28 (93)	69 (82)	97 (85)
Expedited	1 (5)	1 (12)	0	2 (7)	15 (18)	17 (15)

Notes:

[*]Some PIs sponsored more than one protocol.

[†]Since 1 protocol was not a clinical trial, total for analysis was one less than N for notify the PI and further testing.

[‡]Chi-Square analyses were only performed on Notify the PI and the set of All Withdrawal Stipulations Combined, and not performed on ‘Return for another visit’ or ‘Return for further testing’ because of small numbers.

[§]$P < 0.05$,

[°]$P < 0.005$,

[//]$P < 0.0005$.