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Assessment of Consent Capability in Psychiatric and Medical Studies

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Abstract

In order to evaluate psychiatric factors that potentially influence assessment of consent capacity, 195 IRB members read summaries of hypothetical medical (cancer vs. neuropathic pain) and psychiatric trials. They then rated research participants' capacity for consent (capable or not capable), autonomy, and decisional abilities, as well as the legal risk to the institution of the study. Levels of depression information varied across the medical disorders. Significantly fewer IRB members judged participants in the depression trial to possess adequate capacity for consent relative to 4 of 6 medical conditions; legal risk to the institution also was rated higher in the psychiatric study. While IRB members judged participants in depression trials to have less capacity for consent and to pose higher levels of institutional risk than medical trial participants, the addition of increasing information regarding depressive co-morbidities had little or no effect on judgments of medical studies. Implications are discussed relative to the apparent overprotection of participants in psychiatric trials and underprotection of those in medical trials.

Keywords

institutional review boards (IRBs); risk assessment; consent capacity; human subjects protections

Institutional review boards (IRBs) are charged with protecting human research participants, especially minors, prisoners, pregnant women, and people who are mentally disabled (45 CFR 46.111.a.3). Indeed, for the three former groups, regulations spell out specific criteria to guide IRB determination of consent requirements. For the latter group, IRBs are called upon broadly to protect research participants who are thought to have diminished decisional abilities to provide informed consent for research participation or whose consent may be unduly subject to external influences.

While the above mandate seems reasonable, IRBs lack clear mechanisms to guide their determinations. Absent such guidance, IRBs have been accused of being overly paternalistic relative to their assessments of psychiatric trials (Oldham et al., 1999). Similarly, the absence of guidance may impact IRB determinations of trials involving clinical populations where consent-related concerns have not been recognized by statute (Levine et al., 2004; Roberts, 2002). A clear example involves patients with medical conditions (Michaud, Murray, & Bloom, 2001), such as those with cancer (Casarett, Karlawish, & Hirschman, 2003; Miller, 2001; Pereira, Hanson, & Bruera, 1997; Schaeffer et al., 1996) and severe pain (Pearlman et al., 1993; Sullivan et al., 1997). Significant numbers of these patients demonstrate often unrecognized diminished decisional abilities (Raymont et al., 2004) and/or power differentials in the patient-physician relationship that can affect autonomous decision-making (Roberts, 2002). Still others may have unrealistic expectations of benefit from experimental treatment (“therapeutic misconceptions”) (Lidz & Appelbaum, 2002). Indeed, recent research suggests that IRB members may be insensitive to factors such as psychiatric co-morbidities in making categorical judgments of consent capacity—whether potential research participants with primary medical disorders do or do not have the capacity to provide informed, autonomous consent to participate (Luebbert, Tait, Chibnall, & Deshields, 2008).

The present study was designed to address the latter issue directly by asking IRB members to read one of six hypothetical studies of cancer or neuropathic pain, conditions for which depression is a common co-morbidity. Regarding these medical conditions, different levels of information regarding common depressive co-morbidities were provided to IRB members: no depression information; general information indicating that patients in cancer and neuropathic pain studies are at significant risk for depression; or study-specific information indicating that depression is both common and important enough to be included as an outcome variable. IRB member judgments of categorical consent capacity (whether or not the research participant has the capacity to provide informed consent) and other parameters (decisional ability—the ability to understand, appreciate, and weigh study-relevant information, autonomy, and legal risk to the institution) were then compared against judgments made regarding a hypothetical study of major depressive disorder (the reference condition). We expected increasing levels of depression information for the medical disorders to be associated with judgments of decreased categorical consent capacity, decisional abilities, and autonomy, as well as increased judgments of legal risk to the institution.

Methods

Sampling and Response Rate

Through a Freedom of Information Act request, a random sample of 100 U.S. IRB membership lists was drawn from approximately 5,700 IRBs registered with the Office of Human Research Protections in 2006. The 100 IRBs included 1,164 members who were potential participants in the current study. In order to identify e-mail addresses for the latter group, institutions with registered IRBs were contacted, institutional e-mail databases were searched, and potential participants were contacted directly. Through this process, e-mail addresses were obtained for 798 potential participants (68.6% of the total).

Data collection occurred in two waves. In the first wave (April, 2008), e-mails were sent to 476 people, of which 71 (14.9%) were returned as undeliverable/inactive. Of the 405 e-mails that were delivered, 105 (25.9%) participants were accrued. In the second wave (October, 2008), e-mails were sent to the remaining 322 people, of which 33 (10.2%) were returned as undeliverable/inactive. Of the 289 e-mails that were delivered, 90 (31.1%) participants were

accrued. Overall, 195 participants were accrued from 694 contacts, for a response rate of 28.1%.

Study Design

Summaries of seven hypothetical clinical research trials were constructed to represent the seven conditions of the study design. All trials were presented as randomized, placebo-controlled, double-blind, outpatient phase II safety, efficacy, and dose-finding studies of an adjunctive medication. Summaries were ~2.5 pages of single-spaced text and included information typically included in IRB protocols: study purpose, background, study population, inclusion/exclusion criteria, subject role, parameters measured, risks/benefits, research environment, and confidentiality. Summaries described a hypothetical medical study (stage III colon cancer or severe neuropathic pain secondary to diabetes) with varying levels of depression information (none or general information or study-specific information) or a psychiatric study (major depressive disorder). This design yielded seven conditions: (1) cancer/no depression information, (2) pain/no depression information, (3) cancer/general depression information, (4) pain/general depression information, (5) cancer/study-specific depression information, (6) pain/study-specific depression information, and (7) major depressive disorder. Figure 1 displays the study design.

For the general depression information conditions (cancer and pain studies), a single paragraph in the “Background and Description of Patient Population” section described how the relevant patients are at significant risk for major depressive disorder. For the study-specific depression information conditions, the general depression information was augmented with a study outcome variable assessing depression status. While the specific content of summary sections varied (by necessity) across conditions, the nature and amount of information across conditions was kept generally constant. Figure 2 displays the full text of the summaries that represented the seven study conditions.

Procedure

The proposed study was reviewed and approved by a behavioral and social science institutional review board (IRB). Following IRB approval, participants were randomly assigned to one of the seven study conditions when they accessed the study materials through an Internet-based link in a recruitment e-mail. After reading a recruitment statement, participants indicated consent by reading the trial summary and responding to study questions. Participation was anonymous: survey software separated participant responses from identifying information. Mailing information was collected in a separate (unlinked) file and used to send a \$25 reimbursement for participation.

Response Variables

After reading the summary, participants first made estimates of illness severity and functional impairment (0 = very low, 5 = moderate, 10 = very high) for the target patient population. These ratings had previously demonstrated adequate reliability (Luebbert et al., 2008) and were considered potential covariates for the primary analyses.

The primary outcome variable was the IRB member judgment of categorical consent capacity—whether patients eligible for recruitment into the hypothetical trial were or were not capable of providing informed, autonomous consent to participate. This categorical variable was a “no” vs. “yes” judgment.

Other judgments were made regarding the degree to which patients eligible for recruitment into the hypothetical trial would be able to understand, appreciate, and weigh study-relevant information (i.e., decisional ability). Five such questions were derived from a conceptual

model of “decisional capacity” (Appelbaum & Grisso, 1988). Another set of seven questions referenced the degree of autonomy relative to patients’ decisions to participate. These questions assessed the likely effects of a patient’s emotional distress and physical suffering, power differentials in the patient/subject-physician/investigator relationship, and inappropriate patient expectations regarding benefit (Roberts, 2002). A final set of three questions referenced perceived legal risks to the institution of the hypothetical trial, including IRB over-sight requirements. All of these variables were rated on 0-10 scales (0 = not at all/very low; 5 = moderate; 10 = completely/very high/very much). Table 2 in the Results section presents the exact wording of these questions.

Results

Sample Characteristics

The 195 participants were 101 women (51.8%) and 94 men (48.2%). Age was 21-40 years for 29 participants (14.9%), 41-50 years for 56 (28.7%), 51-60 years for 70 (35.9%), and ≥ 61 years for 40 (20.5%). Most participants were Caucasian ($n = 177$, 90.8%), of which 7 (3.9%) were of Hispanic descent. The remaining participants were Asian ($n = 9$, 4.6%), African American ($n = 7$, 3.6%), or Native American ($n = 2$, 1.0%). The highest degree earned was less than college for 2 participants (1.0%), college degree for 23 (11.8%), masters degree for 39 (20.0%), doctorate for 81 (41.5%), and medical (MD/ DO) for 50 (25.6%). Eighty-six participants were university faculty (44.1%), 33 were nonmedical hospital staff (16.9%), 23 were medical hospital staff (11.8%), 19 were administrators (9.7%), 12 were university staff (6.2%), 7 were government employees (3.6%), and 15 were “other” (7.7%). 108 participants were from academic biomedical IRBs (55.4%), 49 from community hospital IRBs (25.1%), 28 from behavioral and social science IRBs (14.4%), and 10 from central IRBs (5.1%).

These sample characteristics were compared across the seven study conditions using chi-squared analysis. Due to limitations of sample size, race and ethnicity comparisons could not be made statistically, and some of the variables had to be collapsed into fewer categories so that all expected frequencies were > 5 for analysis. There were no significant differences associated with gender, $\chi^2(6) = 11.5$, $p = .07$; age (≤ 50 years vs. > 50 years), $\chi^2(6) = 4.9$, $p = .56$; highest degree ($\leq$ masters degree vs. doctorate vs. medical degree), $\chi^2(12) = 15.1$, $p = .24$; position held (university faculty vs. all others), $\chi^2(6) = 1.3$, $p = .97$; or type of IRB (academic biomedical or behavioral/social science vs. community or central), $\chi^2(6) = 7.7$, $p = .26$. These results are consistent with a successful randomization to the experimental conditions.

Primary Analyses

EFFECT OF STUDY CONDITION ON JUDGMENTS OF CATEGORICAL CONSENT CAPACITY

—In the first analysis, logistic regression was used to examine the effect of the seven study conditions on judgments of categorical consent capacity. For the condition variable, the major depressive disorder condition was designated as the reference category (0). Categorical consent capacity was coded as 0 for “not consent capable” vs. 1 for “consent capable.” Initial analyses considered illness severity and functional impairment covariates in the model. Because neither covariate achieved significance, the logistic model was equivalent to a chi-squared test of association, which was significant, $\chi^2(6) = 14.2$, $p < .05$. Post hoc chi-squared comparisons were made between each of the first six conditions and the major depressive disorder condition. Table 1 shows that judgments of categorical consent capacity were higher than the reference condition across all medical conditions, and significantly ($p < .05$) higher in four conditions: cancer/no depression information, pain/ no

depression information, pain/general depression information, and cancer/study-specific depression information.

EFFECT OF STUDY CONDITION ON JUDGMENTS OF DECISIONAL ABILITY, AUTONOMY, AND LEGAL RISK TO THE INSTITUTION—A principal components analysis with varimax rotation was conducted for the 15 decisional ability, autonomy, and institutional legal risk variables to validate the underlying constructs assessed by these variables and to simplify data for further statistical analysis. Table 2 displays a three-factor solution consistent with the conceptually derived subscales. Those factors explained 65.2% of the variance without cross-loadings (based on a minimum loading criterion of 0.35). Factor summary scores were calculated by taking the mean rating of each variable represented in a factor. This yielded scores of 0-10, where higher scores indicated greater perceived threats to autonomy, greater perceived decisional ability, and greater concerns about legal risk to the institution. Internal consistency reliability as assessed by coefficient alpha was acceptable for all factors: 0.86 for threats to autonomy, 0.89 for decisional ability, and 0.79 for institutional legal risk.

Differences in ratings on the three summary scores were evaluated across the seven study conditions using multivariate analysis of covariance (MANCOVA), with follow-up univariate ANCOVA when indicated. Post hoc comparisons were simple contrasts, where each of the first six conditions was compared against the major depressive disorder condition. Initial analyses included the illness severity and functional impairment covariates. The multivariate main effect for study condition was significant in the MANCOVA [Wilks' $\lambda = 0.85$, $p < .05$], as was the illness severity covariate [Wilks' $\lambda = 0.86$, $p < .001$]. Follow-up ANCOVAs indicated that illness severity was a significant covariate with respect to judgments of threats to autonomy [$F(1,187) = 14.7$, $p < .001$] and institutional legal risk [$F(1,187) = 15.0$, $p < .001$]. ANCOVA analyses also indicated that the main effect for condition was significant only for institutional legal risk [$F(6,187) = 2.4$, $p < .05$]. Post hoc simple contrasts indicated that IRB members showed significantly ($p < .05$) more concern about legal risk to the institution for the major depressive disorder condition, relative to five of the other six conditions: cancer/no depression information, pain/no depression information, cancer/general depression information, pain/general depression information, and cancer/study-specific depression information conditions. Table 3 displays the results of these analyses.

ASSOCIATIONS BETWEEN JUDGMENTS OF CATEGORICAL CONSENT CAPACITY AND JUDGMENTS OF THREATS TO AUTONOMY, DECISIONAL ABILITY, AND INSTITUTIONAL LEGAL RISK—Logistic regression analysis was used to examine these associations across study conditions. As before, categorical consent capacity was dichotomous (0 vs. 1), while summary scores for threats to autonomy, decisional ability, and institutional legal risk were continuous variables. Illness severity and functional impairment were not significant covariates in the model. The logistic regression equation with the three summary scores was significant [$\chi^2(3) = 32.6$, $p < .001$]. As displayed in Table 4, only higher scores for perceived institutional legal risk were associated with greater odds of a determination of “not consent capable.”

Discussion

Consistent with prior research (Luebbert et al., 2008), the results of the present study showed IRB members to view persons participating in a hypothetical treatment study of major depressive disorder as less likely to have the capacity to provide informed consent than patients participating in medical trials, even medical conditions with a high incidence of co-morbid depression. Increasing information regarding the possibility and importance of

co-morbid depression did not consistently affect IRB member judgments of categorical consent capacity for the two medical conditions. For cancer trials, an inconsistent pattern emerged: levels of categorical consent capacity were comparable to the major depression trial for the general depression condition, but not for the no-information or study-specific conditions. The three pain trials followed the hypothesized pattern more closely, with IRB members judging categorical consent capacity as comparable to the major depression trial when study-specific depression information was included.

The results for the institutional legal risk variables followed a similar pattern. The major depression trial was viewed as posing the highest legal risk to the institution. Across all levels of depression salience, cancer trials were viewed as posing significantly less institutional legal risk than the major depression trial. For the neuropathic pain trials, only the trial that included study-specific depression information yielded an assessment of legal risk to the institution similar to the major depression trial, a pattern that was consistent with the consent capacity results.

Results for the decisional ability and autonomy scales across the study conditions showed no differences between the medical trials and the depression trial. Consistent with these results, neither ratings of decisional ability nor threats to autonomy predicted categorical consent capacity across the study conditions. Clearly, IRB member judgments of subject autonomy and decisional ability were not influenced by the varying levels of depression information that were included in the cancer and neuropathic pain studies. Instead, categorical consent capacity was associated only with IRB member ratings of institutional legal risk.

The patterns described above clearly show that IRB members viewed the consent capacity and institutional risk profiles of psychiatric studies as problematic relative to those of medical studies. Moreover, this pattern held even when substantial information about the importance of psychiatric co-morbidities was added to the latter studies. In the context of a similar pattern that was reported in a previous study (Luebbert et al., 2008), the results suggest that negative attitudes toward psychiatric research influence judgments made by IRB members. Further, the lack of association between judgments of categorical consent capacity and ratings of decisional ability or autonomy suggests that such judgments are driven largely by concerns regarding legal risk to institutions, rather than concerns about the decisional abilities or autonomy of the participants, themselves. While the latter explanation would seem to be inconsistent with the mandate that IRBs focus on the protection of human subjects, it suggests that IRB members are susceptible to commonly held views of psychiatric patients as potentially dangerous and unpredictable (Corrigan & Wassel, 2008). Such views also could predispose IRBs to assume a paternalistic stance toward psychiatric studies and potentially inhibit the conduct of research on mental disorders (Oldham, Haimowitz, & Delano, 1999).

Aside from the implications of this research for the statutory obligations of IRBs, the patterns described above seem inconsistent with the available research on consent capacity and psychiatric research. Evidence specific to consent capacity in depression has shown that depressed outpatients demonstrate relatively unimpaired decision-making abilities related to research participation (Appelbaum et al., 1999). Moreover, other evidence has shown that even patients with such severe conditions as schizophrenia can provide competent consent as long as they are exposed to adequate educational materials (Carpenter et al., 2000; Moser et al., 2002).

Although less clear than the results relative to the psychiatric condition, the data also suggest that IRB members viewed the institutional legal risk and consent capacity profiles of participants in the pain and cancer trials somewhat differently. For the cancer trials, IRB

members demonstrated little concern regarding trial-related legal risk or consent capacity issues, regardless of the level of the depression variable. For participants in pain trials, however, IRB members viewed the legal risk/consent issues posed by a trial with depression-specific information as comparable to those posed by the depression trial, while participants in the lower salience conditions were viewed more benignly. Thus, the depression information seemed to influence legal risk/consent judgments for the pain trials more than the cancer trials. While the study was not designed to explain why this phenomenon occurred, we speculate that IRB members may have been influenced by the perceived “prestige” of the condition under study (Album & Westin, 2008). In the case of conditions such as cancer, the validity of disease-related symptoms is seldom questioned (i.e., symptoms typically correlate with specific, observable medical evidence) and the disorder is seen as potentially life-threatening. Both of these considerations support the inherent validity of the disorder and of related symptoms, making cancer a high-prestige disorder. For pain disorders, however, symptoms are primarily subjective, often poorly correlated with objective medical evidence, and not directly life-threatening. These considerations raise questions about the validity of the disorder and of related symptoms (Tait, Chibnall, & Kalauokalani, 2009), making intractable pain a low-prestige condition, particularly when coupled with a similarly low-prestige psychiatric disorder. Hence, considerations of medical prestige may mediate IRB member judgments of categorical consent capacity and institutional legal risk: when perceived prestige is high, the relative impact of psychiatric co-morbidities may be discounted, while the impact of such co-morbidities may be greater when perceived prestige is low. Obviously, research is needed to evaluate the above speculation.

It is also important to note the absence of effects associated with decisional ability. Decisional ability is an essential element of the consent process upon which hinges many statutory protections (Kipnis, 2001; Berg & Appelbaum, 1999). In this study, judgments of the decisional ability of potential trial participants did not differ as a function of the study conditions, even though major depression is recognized as a neuropsychiatric condition that can have measurable cognitive sequelae (Baker & Channon, 1995). Moreover, even across study conditions, IRB members’ decisions about categorical consent capacity did not correlate with their assessments of decisional ability. A very different pattern could have emerged if the disorder involved a primary loss of cognitive capacity (e.g., Alzheimer’s disease, schizophrenia). Nonetheless, it is interesting that IRB members apparently did not consider decisional ability (or, at least, weigh it heavily) when assessing categorical consent capacity. Further research is needed to determine whether this finding is study specific or, instead, a finding that applies across clinical studies.

Limitations of this study should be considered when interpreting these findings. First, the response rate was somewhat low. While this problem is mitigated by the study design (it was not designed to establish normative standards), the impact of the response rate on results is unknown. Similarly, the study involved abstracts of hypothetical studies to which IRB members responded individually, not through group discussion. Because the information provided to study participants was necessarily brief and the participants did not have the benefit of others’ perspectives, the data presented herein diverge considerably from standard IRB practice wherein group discussion can influence member judgments. Finally, the study materials were presented in an Internet format, a format that may yield less differentiation on rating scales than a face-to-face format (Heerwegh & Loosveldt, 2008). Hence, it is difficult to assess whether the study presentation of depression information was as impactful as it might have been if delivered via other formats.

Notwithstanding these limitations, the current results echo previous findings that have shown that participants in psychiatric trials are likely to be viewed as less capable of

informed consent than participants in medical trials (Luebbert et al., 2008). The data suggest that IRB members view psychiatric studies negatively and that these concerns are significantly linked to concerns related to legal risk to institutions, rather than concerns about decisional ability and autonomy. The results also indicate that IRB members are relatively insensitive to issues of categorical consent capacity, decisional ability, autonomy, and institutional legal risk in medical studies. Taken together, the data suggest that IRBs are overly protective of participants in psychiatric research; they may also be underprotective of patients in medical research with significant psychiatric co-morbidities. Clearly, there is a need for further research that targets factors affecting IRB decision-making in psychiatric and medical studies, especially as those factors may impact on the primary IRB mission, the protection of participants in research.

Best Practices

The results of this study provide further support for the presence of systematic differences in how IRB members evaluate consent capacity and legal risk to institutions in clinical research. While IRB members were quite sensitive to such issues in bona fide psychiatric studies, that sensitivity did not extend to medical studies. Even when the assessment of psychiatric co-morbidities was included as a study aim, IRB members evinced little concern for consent capacity and institutional legal risk for participants in medical studies, especially cancer trials. These results strongly suggest that IRBs are overly concerned with the protection of human subjects in psychiatric studies. While less clear, the data also suggest that IRB members may be inadequately attentive to threats to consent capacity in medical studies. To address the former issue, IRBs may need to be better educated about the research that has shown participants in psychiatric trials to be capable of providing an informed consent when provided with adequate information. In addition, in an effort to address both issues, perhaps, protocol reviews and meeting processes should be structured so as to insure that issues related to consent capacity, decisional ability, threats to autonomy, and risks to prospective research participants (separate from legal risk to institutions) are addressed explicitly in the discussion.

Research Agenda

Because IRBs serve as the primary mechanism for ethical oversight in clinical research, data that suggest inconsistencies in practice are of concern when those inconsistencies may inhibit the conduct of needed research or place selected patient groups at increased risk. To date, studies of IRB decision-making have used analog methodologies, dependent on written research vignettes, as a means for study. While analog studies have the advantages of clear experimental design and measurement, they lack fidelity in replicating such complex processes as the group decision-making that characterizes IRB meetings. To determine whether the results of the analog studies apply to practice, research is needed that examines actual IRB discussions of psychiatric and medical studies, as well as research that considers both discussion processes and outcomes.

Educational Implications

Two educational needs emerge from this research, one bearing on its implications for psychiatric studies and the other on its implications for medical studies. Relative to the former, the data clearly show exquisite sensitivity among IRB members to the consent capacity of psychiatric patients, as well as the level of institutional risk associated with research involving such patients. While this sensitivity may be consistent with federal statutes, there is evidence that even patients with severe psychiatric morbidities (e.g., schizophrenia) have the capacity for informed consent so long as the consenting process is handled in a manner that maximizes their understanding of the research process (see, e.g., Carpenter et al., 2000; Dunn et al., 2002; Jeste et al., 2008; Misra et al., 2010). Given the

available data, the sensitivity demonstrated by IRB members in this and other studies may inhibit the conduct of psychiatric research. There is a need for education of investigators who are involved in research with such participants as to the most effective approaches to conducting the consent process, as well as education of IRB members as to the efficacy of such processes when appropriately administered.

Relative to medical studies, the data suggest that research participants with cancer and comorbid depression are viewed with little concern for consent capacity. Despite the relative lack of concern, such participants could be compromised secondary to a variety of possible concerns, including the gravity of their medical condition, the associated potential for therapeutic misconception, and the patient-provider power differential inherent in the treatment of a potentially fatal condition, as well as the neuropsychiatric sequelae of treatment or comorbid mood disorders. While each of these risks could be managed with a well-constructed research protocol, the lack of sensitivity to these issues is cause for concern and a call for education.

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Authors' Biographical Sketches

Raymond Tait is Vice President for Research and Professor of Neurology & Psychiatry at Saint Louis University. He has chaired the Institutional Review Board and the university's Conflict of Interest Committee. In the latter role, he observed inconsistencies in the handling of medical and psychiatric research and in the levels of attention paid to vulnerable subjects; these observations helped to frame the study question. He was involved in the design of this project, as well as data collection, data analysis and interpretation, and in writing/revising the manuscript.

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Level of Depression Variable	Colon Cancer	Neuropathic Pain	Major Depressive Disorder
No depression information	X	X	
General depression information	X	X	
Depression as study variable	X	X	X

Fig. 1.

Study design, including levels of the depression information variable and the major depression comparator.

<p>Purpose: This is a phase II (safety, efficacy, and dose-finding), double blind, randomized, outpatient trial of a new [chemotherapy (A1,B1,C1) / neuroprotective (A2,B2,C2) / antidepressant (C3)] agent, Drug X. Its intended indication is for use in [stage III colon cancer / severe neuropathic pain / major depressive disorder]. Drug X is an adjunctive treatment that is designed to augment the effects of standard [chemotherapy / neuroprotective / antidepressant] agents. A total of approximately 360 subjects across multiple investigational centers will be recruited into this trial. Subjects will be randomized in a 1:1 ratio to either Drug X or placebo. The purpose of the trial is to evaluate the effect of Drug X, relative to placebo, [on cancer recurrence in patients who have undergone surgical resection of a colon tumor, and are scheduled to receive standard chemotherapy / on severe neuropathic pain in patients who are taking standard neuroprotective agents / in patients with major depressive disorder who are receiving standard antidepressant treatment].</p> <p>(C1, C2)</p> <p>A further purpose of the trial is to monitor the quality of life of subjects, including the prevalence and incidence of major depressive disorder over the course of the trial.</p> <p>(All summaries)</p> <p>Research Environment: Participation will occur on an outpatient basis encompassing 10 visits (including screening) to the hospital and a total treatment duration of 24 weeks (including screening, total participation time is 26 weeks).</p>	
<p>(A1, B1, C1)</p> <p>Background and Description of Patient Population: Subjects will be male and female patients with stage III colon cancer. Colorectal cancer is the third most common cancer found in men and women in the US. The American Cancer Society estimates an annual incidence rate of about 106,680 new cases of colon cancer and 41,930 new cases of rectal cancer in the US in 2006. Combined, these cancers will likely cause about 55,370 deaths in 2006. The five-year relative survival rate is 90% for people whose colorectal cancer is treated in an early stage, before it has metastasized. However, only 39% of colorectal cancers are found at that early stage. For stage III colon cancer, the five-year relative survival rate ranges from 44% to 83%, depending on the substage.</p> <p>Typical risk factors for colorectal cancer include a history or current diagnosis of colorectal polyps, chronic inflammatory bowel disease, and/or diabetes (30-40% increased risk of colorectal cancer). Other important factors include a diet high in fat (primarily from animal sources), physical inactivity, obesity, tobacco use, and alcohol abuse/dependence.</p> <p>(C3)</p> <p>Background and Description of Patient Population: Subjects will be male and female patients with major depressive disorder. Major depressive disorder is a common diagnosis in persons seeking psychiatric treatment and affects approximately 5.3% of all adults in the US. It is estimated that 1 in 5 women and 1 in 15 men will experience a major depressive disorder in their lifetime. Left untreated, ~40% of persons with major depressive disorder will have significant symptoms of depression one year later. Prevalence of the first episode of major depressive disorder peaks at age 25-30 for men and age 15-20 for women. Depression is the primary risk factor for suicide and/or suicidal behavior.</p> <p>Typical risk factors for major depressive disorder include a family history of depression, female gender, substance abuse, significant adverse life events (e.g., death of a loved one, divorce, job loss), certain personality characteristics, certain endocrine or metabolic abnormalities, and significant medical conditions (particularly as condition severity and duration increase). The latter risk factor is a function of the combined effects of physical discomfort, disease-imposed restrictions on activities of daily living (including work, recreation, family, etc.), disease-imposed interference with significant relationships (including social activities, sexual functioning, etc.), concerns about the future course of the illness, and loss of hope. The presence of depression has been shown to significantly increase morbidity and decrease overall quality of life in medically ill patients.</p> <p>(B1, B2, C1, C2)</p> <p>Quality of life may also be compromised in colorectal cancer patients/patients with severe neuropathic pain. Major depressive disorder, in particular, is common in patients with [colorectal cancer/severe neuropathic pain]. The prevalence of depression increases significantly as the severity and duration of the [cancer/pain increase]. Depression in this population is related to the combined effects of physical discomfort, disease-imposed restrictions on activities of daily living (including work, recreation, family, etc.), disease-imposed interference with significant relationships (including social activities, sexual functioning, etc.), concerns about the future course of the illness, and loss of hope. The presence of depression has been shown to significantly increase morbidity and decrease overall quality of life in [colorectal cancer patients/patients with severe neuropathic pain].</p>	<p>(A2, B2, C2)</p> <p>Background and Description of Patient Population: Subjects will be male and female patients with severe neuropathic pain (usual pain severity of greater than or equal to 7 on a 0-10 scale, with significant impairment of function due to pain). While the exact number is unknown, it is estimated that over 3 million Americans experience neuropathic pain, resulting from nerve damage. Neuropathic pain is usually characterized as electric, burning, icy cold, frostbite-like, aching, tingling, and needles and pins. The pain sensations generally begin in the feet; later affecting the legs and/or hands. Other signs of neuropathy include sensory loss, allodynia (pain from normally non-painful stimulation), and hyperpathia (an exaggerated pain response). Severe neuropathic pain is associated with significant disability in the performance of activities of daily living, including home- and work-related activities.</p> <p>Typical risk factors for severe neuropathic pain include a history of poorly controlled diabetes, herpes simplex infection, and/or trauma resulting in nerve injury.</p>
<p>(A1, B1, C1)</p> <p>Standard of care for stage III colon cancer is surgical resection, followed by 24 weeks of chemotherapy. Radiation treatment may or may not be warranted, depending on the degree of involvement of adjacent tissues.</p> <p>(C3)</p> <p>Standard of care for major depressive disorder is treatment with an antidepressant medication of known efficacy (e.g., SSRIs) for a minimum of 6 months. Psychotherapy may be used as an adjunct to pharmacotherapy.</p> <p>(A1, B1, C1)</p> <p>Inclusion and Exclusion Criteria: Primary inclusion criteria include: (a) Male or female, between 18 and 55 years of age; (b) Diagnosis of stage III colon cancer, as defined by the following parameters according to TNM classification: (b1) Any stage III tumor, (b2) Involvement of 1-4 lymph nodes, (b3) No evidence of distant metastases; (c) Colon cancer surgery within previous 8 weeks.</p> <p>Primary exclusion criteria include: (a) Previous chemotherapy or radiation therapy for colon cancer; (b) Pre-existing ischemic heart disease, cardiac failure, or liver disease (acute or chronic); (c) Preexisting or concomitant neoplasm; (d) Current anemia, leukopenia, or thrombopenia; (e) Known or suspected adverse sensitivity to Drug X; (f) Pregnancy or lactation.</p> <p>Parameters to be Measured: Primary cancer-related outcome parameters include periodic routine physical examinations (to assess body-mass index, blood pressure, heart rate, etc.), laboratory assays (to evaluate chemistry and hematology levels), chest radiographs (to detect the presence of lung metastases), abdominal ultrasound (to detect the presence of tumor recurrence), colonoscopy (to detect further tumors and polyps), and carcinoembryonic antigen assays (to examine protein assay, cancer recurrence, and detect metastases).</p> <p>(C3)</p> <p>Inclusion and Exclusion Criteria: Primary inclusion criteria include (a) male or female, between 18 and 55 years of age; (b) Diagnosis of major depressive disorder, as defined by the following DSM-IV parameters: (b1) Depressed mood, with diminished interest in usual activities, (b2) decreased appetite and/or weight loss, (b3) sleep disturbance, (b4) psychomotor agitation or retardation, (b5) fatigue, (b6) poor concentration, (b7) feelings of worthlessness and/or guilt; (c) Symptoms of depression are present for at least 4 weeks.</p> <p>Primary exclusion criteria include (a) Electroconvulsive therapy in the previous 6 months; (b) History of alcohol or substance abuse within the past three years; (c) History of myocardial infarction or cardiac arrest; (d) History of schizophrenia, schizoaffective disorder, or psychotic depression; (e) Known or suspected adverse sensitivity to Drug X; (f) Pregnancy or lactation.</p> <p>Parameters to be Measured:</p> <p>Primary depression-related outcome parameters will be the presence and severity of major depressive disorder as assessed by the clinician-administered Hamilton Depression Rating Scale Interview (a very comprehensive instrument that examines somatic, cognitive, and mood-related aspects of depression and that typically requires a 30-45' interview by an experienced clinician) and by subject self-report on the Center for Epidemiologic Studies Depression Scale (a 20-item self-report instrument that focuses on vegetative and mood-related aspects of depression and that typically requires 5-10'). A secondary depression-related parameter will be change in severity of depression symptoms as assessed by the clinician-completed Clinical Global Impression of Change Scale.</p> <p>(C1, C2)</p> <p>The presence and severity of major depressive disorder will be assessed by the clinician-administered Hamilton Depression Rating Scale interview (a very comprehensive instrument that examines somatic, cognitive, and mood-related aspects of depression and that typically requires a 30-45' interview by an experienced clinician) and by subject self-report on the Center for Epidemiologic Studies Depression Scale (a 20-item self-report instrument that focuses on vegetative and mood-related aspects of depression and that typically requires 5-10'). Based on established cut-off scores for clinical significance, scores on either parameter indicative of a major depressive episode will result in a diagnostic clinical interview by a psychiatrist for confirmation of diagnosis.</p>	<p>(A2, B2, C2)</p> <p>Standard of care for severe neuropathic pain is anti-convulsant medication (patients may derive benefit from any of several marketed anti-convulsants). If unresponsive to anti-convulsants, opioid therapy may be warranted.</p> <p>(A2, B2, C2)</p> <p>Inclusion and Exclusion Criteria: Primary inclusion criteria include: (a) Male or female, between 18 and 55 years of age; (b) Severe neuropathic pain defined by the following parameters: (b1) Pain of six months or greater, supported by positive nerve conduction findings, in feet, hands, and/or other areas (with or without numbness, tingling, or diminished sensation), (b2) Usual pain severity of greater than or equal to 7 on a 0-10 scale, with significant impairment of functional abilities secondary to pain, (b3) Vitamin B12 and folate levels within normal limits; (c) Ability to maintain pre-study pain medications/dosages and therapies (e.g., physical therapy, biofeedback, relaxation, hypnosis) for duration of the clinical trial (26 weeks)</p> <p>Primary exclusion criteria include: (a) Any condition that confounds the diagnosis of neuropathy, including hereditary neuropathy or compression-related neuropathy, poorly controlled diabetes, and vitamin B12 deficiency; (b) Use of transcutaneous electrical nerve stimulation (TENS) with inability to discontinue for duration of clinical trial; (c) Any amputation (other than toes); (d) History of alcohol or substance abuse within the past three years; (e) Known or suspected adverse sensitivity to Drug X; (f) Pregnancy or lactation.</p> <p>Parameters to be Measured: Primary pain-related outcome parameters include pain ratings—based on standardized visual analog scales—of pain intensity (how much the pain hurts) and pain affect (unpleasantness of the pain). Daily ratings will be made in a pain diary of minimum, maximum, and usual levels of pain intensity and pain affect. Concomitant analgesic use also will be recorded as an indirect indicator of pain severity. Sensory function will be examined by measurements of touch detection thresholds.</p>

(All summaries)
 Safety will be monitored through periodic routine physical examinations, laboratory assays (to evaluate chemistry and hematology levels), liver function tests (to rule out hepatic abnormality), vitamin B12 and folate levels (to rule out vitamin deficiency), and electrocardiograms (to evaluate cardiac conduction).
Role of subjects: Eligible patients will receive [a one-hour continuous infusion (A1,B1,C1) / daily doses (A2,B2,C2) / daily doses (C3)] of Drug X or placebo that is administered concurrently with their standard [chemotherapy / neuroprotective / antidepressant] regimen. Patients will receive [8 infusions / one dose per day / one dose per day] over a course of 24 weeks. Visits and assessments will be at screening, baseline, and weeks 3, 6, 9, 12, 15, 18, 21, and 24. Total duration of subject participation will be 26 weeks (including screening).
Potential Study Risks: Treatment will be ineffective; Side effects of Drug X, including fatigue, nervousness, nausea, headache, insomnia, dry mouth, tremors, dizziness, loss of appetite; significant cardiovascular complications; endocrine or hepatic abnormality associated with Drug X; Loss of confidentiality.
Potential Study Benefits: To patients: Potential to reduce likelihood of [cancer recurrence (A1,B1,C1) / pain intensity levels (A2,B2,C2) / severity of major depressive disorder(C3)] as a result of treatment efficacy.
(C1, C2)
 Identification of (and subsequent referral for treatment of) major depressive disorder.
 To society: Establishing the efficacy and safety of Drug X for [colon cancer (A1,B1,C1) / neuropathic pain (A2,B2,C2) / major depressive disorder (C3)].
(C1, C2)
 Better understanding of the prevalence, incidence, and significance of major depressive disorder in [stage III colon cancer patients / patients with severe neuropathic pain].
(All summaries)
 Confidentiality: Confidentiality will be protected by assigning coded identifiers to subjects and maintaining the master list linking the names in a separate, locked file cabinet. Access to the records will be limited to the research team and authorized entities.

Fig. 2.

Text of summaries representing the seven study conditions: A1 = cancer/no depression information; A2 = neuropathic pain/no depression information; B1 = cancer/general depression information; B2 = neuropathic pain/general depression information; C1 = cancer/study-specific depression information; C2 = neuropathic pain/study-specific depression information; and C3 = major depressive disorder. Information in brackets [] varied across summaries. Information in braces { } indicates the condition in which the information appeared. Order of information as presented here was the order of information in the actual summaries.

TABLE 1

Effect of Study Condition on Judgments of Consent Capability.

Study Conditions	Consent Capable Pct. (n) Judged
Cancer/No Depression Information	96.2% (25)*
Pain/No Depression Information	87.9% (29)*
Cancer/General Depression Information	79.3% (23)
Pain/General Depression Information	96.3% (26)*
Cancer/Study-Specific Depression Information	92.3% (24)*
Pain/Study-Specific Depression Information	83.3% (25)
Major Depressive Disorder	66.7% (16)

* $p < .05$ compared to Major Depressive Disorder.

TABLE 2

Principal Components Analysis of Judgment Variables.

Judgment Variables	Vulnerability (25.5%) ^a	Decisional Capacity (24.2%)	Institutional Risk (15.4%)
When making the decision to participate or not, to what degree is this type of patient ...			
... vulnerable to influence by the recruiting investigator?	0.73	—	—
... likely to be swayed toward participation by desperation for treatment?	0.83	—	—
... likely to be swayed toward participation by desperation over relief of suffering?	0.71	—	—
... likely to be swayed toward participation by a desire to acquiesce to the needs of the recruiting investigator?	0.57	—	—
... vulnerable to inappropriately high expectations regarding the benefits of participation?	0.74	—	—
Undue influence is defined as the process of exerting influence or pressure on a person to act, or refrain from acting, contrary to free choice. In research, this may take the form of verbal persuasion or inducement to participate in a study. What level of risk of undue influence exists in this study with this type of patient?	0.71	—	—
How vulnerable is this type of patient to undue influence?	0.81	—	—
To what degree will a patient recruited for this trial be able to ...			
... understand the purpose of the trial?	—	0.77	—
... understand the risks/benefits of participation, relative to standard care?	—	0.83	—
... appreciate the impact of trial procedures (e.g., double blind design, randomization, use of investigational drug) on his/her medical care during the trial?	—	0.77	—
... rationally weigh the potential benefits of the trial against the potential risks of the trial?	—	0.88	—
... rationally weigh the potential risks posed by the side effects of the trial medication against potential benefits of the trial?	—	0.87	—
I have concerns regarding the legal risk to the institution (e.g., potential for a lawsuit) that this type of study might pose.	—	—	0.87
The level of IRB oversight for this type of study should be higher than the customary level (e.g., the period of approval should be shorter).	—	—	0.76
What is the level of legal risk to the institution for conducting this study?	—	—	0.81

^aPercentage of variance accounted for by the factor.

TABLE 3
Effect of Study Condition on Judgments of Vulnerability, Decisional Capacity, and Institutional Risk.

Study Conditions	Mean (95% CI)		
	Vulnerability	Decisional Capacity	Institutional Risk [*]
Cancer/No Depression Information	6.3 (5.7-6.9)	5.0 (4.2-5.8)	2.9 (2.1-3.7) ^a
Pain/No Depression Information	6.7 (6.2-7.2)	5.9 (5.2-6.6)	3.4 (2.7-4.1) ^a
Cancer/General Depression Information	6.2 (5.7-6.8)	5.9 (5.2-6.6)	3.0 (2.3-3.8) ^a
Pain/General Depression Information	6.8 (6.2-7.4)	6.2 (5.4-7.0)	3.1 (2.3-3.9) ^a
Cancer/Study-Specific Depression Information	6.5 (6.0-7.1)	6.0 (5.3-6.8)	3.1 (2.3-3.9) ^a
Pain/Study-Specific Depression Information	7.1 (6.6-7.7)	5.5 (4.8-6.2)	3.7 (3.0-4.8)
Major Depressive Disorder	6.8 (6.2-7.4)	5.2 (4.4-6.0)	4.7 (3.9-5.6)

Note: Means and confidence intervals (CI) are adjusted for the covariate of illness severity.

*
p < .05.

^aSignificantly different ($p < .05$) from Major Depressive Disorder condition by simple contrast.

TABLE 4

Logistic Regression Results: Association of Judgment Variables with Consent Capability.

Judgment Variables	Odds Ratio	95% CI
Vulnerability	0.74	0.51-1.09
Decisional Capacity	1.01	0.78-1.32
Institutional Risk	0.61*	0.48-0.78

Note: Consent capability was the criterion variable: 0 = not consent capable; 1 = consent capable

*
p < .001.