Published in final edited form as:

J Psychiatr Res. 2014 September ; 56: 90–97. doi:10.1016/j.jpsychires.2014.05.007.

Giving Voice to Study Volunteers: Comparing views of mentally ill, physically ill, and healthy protocol participants on ethical aspects of clinical research

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Abstract

Motivation—Ethical controversy surrounds clinical research involving seriously ill participants. While many stakeholders have opinions, the extent to which protocol volunteers themselves see human research as ethically acceptable has not been documented. To address this gap of knowledge, authors sought to assess views of healthy and ill clinical research volunteers regarding the ethical acceptability of human studies involving individuals who are ill or are potentially vulnerable.

Methods—Surveys and semi-structured interviews were used to query clinical research protocol participants and a comparison group of healthy individuals. A total of 179 respondents participated in this study: 150 in protocols (60 mentally ill, 43 physically ill, and 47 healthy clinical research protocol participants) and 29 healthy individuals not enrolled in protocols. Main outcome measures included responses regarding ethical acceptability of clinical research when it presents significant burdens and risks, involves people with serious mental and physical illness, or enrolls people with other potential vulnerabilities in the research situation.

Results—Respondents expressed decreasing levels of acceptance of participation in research that posed burdens of increasing severity. Participation in protocols with possibly life-threatening consequences was perceived as least acceptable (mean = 1.82, sd = 1.29). Research on serious

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The author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

My coauthor and I have no conflicts of interest to disclose.

Contributors

Author Dr. Laura Roberts designed the study and wrote the protocol, managed the literature searches and analyses. Author Dr. Jane Kim managed and undertook the statistical analyses, and Dr. Laura Roberts wrote the first draft of the manuscript. Both authors contributed to and have approved the final manuscript.

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illnesses, including HIV, cancer, schizophrenia, depression, and post-traumatic stress disorder, was seen as ethically acceptable across respondent groups (range of means = [4.0, 4.7]). Mentally ill volunteers expressed levels of ethical acceptability for physical illness research and mental illness research as acceptable and similar, while physically ill volunteers expressed greater ethical acceptability for physical illness research than for mental illness research. Mentally ill, physically ill, and healthy participants expressed neutral to favorable perspectives regarding the ethical acceptability of clinical research participation by potentially vulnerable subpopulations (difference in acceptability perceived by mentally ill - healthy = -0.04, CI [-0.46, 0.39]; physically ill - healthy = -0.13, CI [-0.62, -0.36]).

Conclusions—Clinical research volunteers and healthy clinical research-“naive” individuals view studies involving ill people as ethically acceptable, and their responses reflect concern regarding research that poses considerable burdens and risks and research involving vulnerable subpopulations. Physically ill research volunteers may be more willing to see burdensome and risky research as acceptable. Mentally ill research volunteers and healthy individuals expressed similar perspectives in this study, helping to dispel a misconception that those with mental illness should be presumed to hold disparate views.

INTRODUCTION

Clinical research seeks to develop new knowledge to better understand and to formulate better treatments for serious illnesses that give rise to great personal suffering and represent a burden to the public health. Many thousands of clinical research protocols are underway throughout the world.¹ These protocols may produce valuable data regarding new treatments and inspire hope for a better future, and yet their conduct is ethically sensitive because they necessarily involve people who live with significant symptoms or deficits, who may feel desperate, and who may have few options for adequate care.^{2–6} Moreover, many worry that people with certain illnesses such as schizophrenia or HIV may never be able to participate fully in the clinical research process without the potential for exploitation, due to stigma and the nature of these diseases.³⁶ Indeed, concerns have persisted for decades regarding the ethical acceptability of including people with different illnesses or have characteristics that may make them especially vulnerable in the context of human studies.^{17–19}

Amidst the controversy and concerns surrounding clinical research, very little is known about the perspectives held by the very individuals who are personally affected with illness and whose participation is essential to the conduct of clinical research – namely, people living with serious illness and healthy people who are willing to volunteer for human studies. Learning the distinct perspectives of ill individuals who may be recruited into research protocols is vital to fulfilling the fundamental ethical principles of respect for persons, beneficence, and justice, upon which human research is predicated.^{20,21–27} Understanding these perspectives is important for investigators who are entrusted with the conduct of human studies as well as for policy makers who establish the overarching societal framework of safeguards for scientific experimentation. Nevertheless, few data exist to help guide stakeholders in the research process regarding attitudes of seriously ill people who volunteer to participate in clinical research protocols.

To address this gap, the lead author with colleagues undertook a study to determine the attitudes of clinical research participants and to compare the perspectives expressed by participants with physical illness, with mental illness, and in good health. In this paper we sought to assess the ethical acceptability for human research as endorsed by clinical research participants, and to examine the degree to which perspectives expressed by seriously ill individuals differ from those of healthy individuals. Furthermore, we sought to explore the degree to which ill individuals express attitudes that were sensitive to the potential vulnerabilities of certain subpopulations that may emerge in the research situation (e.g., conditions and attributes) and their acceptance of participation in the context of protocol-related burdens ranging from mild severity to life-threatening danger. As a secondary exploratory aim, we explored whether and how the experience of being in a protocol may shape perspectives on clinical research.

METHODS

Study population

Eligible study participants included volunteers in clinical protocols at the University of New Mexico School of Medicine with a concurrent primary diagnosis of schizophrenia, depression or anxiety, cancer, HIV, or were in good health. Healthy comparison subjects, who were either enrolled in a clinical protocol or not enrolled in a clinical research protocol, were recruited at the University of New Mexico Health Sciences Center and various clinics. Participants with active substance dependence were excluded from the study. In total, 103 respondents with illness consented to the study, and 76 healthy respondents consented to the study.

Survey Instrument

We created and pilot tested a questionnaire to assess views of ethically important aspects of clinical research, based on our previous work^{24–26,28} and the existing research ethics and informed consent literatures. The resultant 301-item survey was administered along with the Brief Symptom Inventory (BSI), Short Form-36 (SF-36), Social Support Survey (SSS), Multidimensional Health Locus of Control (MHLOC), and an open-ended structured interview of 23 questions.

Procedure

We obtained written informed consent for our project. No information from our project was shared with the clinical research teams. This IRB-approved study was funded by the National Institute of Mental Health and the National Institute on Drug Abuse. Interviews for our “piggy back” project were conducted within 7 days of their informed consent disclosure session for their respective clinical protocols. The survey and interview session was completed, on average, in 1.5 to 2 hours. Participants received \$25 compensation.

Main outcome measures

Respondents were queried on the ethical acceptability of research in three situations or domains. Items in domain 1 assessing the ethical acceptability of research participation in the protocol burdens were rated on a 5-point scale (1=“strongly disagree,” 5= “strongly

agree”). In domain 2, respondents rated the ethical acceptability of research participation (1=“absolutely not acceptable”, 5=“absolutely acceptable”) involving people with cancer, HIV, depression, schizophrenia or post-traumatic stress disorder. In domain 3, respondents rated the ethical acceptability of research involving populations with illness-related vulnerabilities and with potential vulnerabilities not related to illness.

Statistical Methods

Our primary aim is to examine and compare the views of protocol volunteers with mental illness, physical illness, and in good health, while adjusting for all potential confounders, such as age, gender, race/ethnicity, education level. As a secondary aim, we explored whether enrollment in a clinical research protocol is associated with different views regarding ethical acceptability of research.

Covariates in this study are sex, age, education, race/ethnicity. Age was dichotomized at 50 years of age, and education was dichotomized into having completed college or more, versus having completed some college or less. Race/ethnicity categories were White, Hispanic, and other underrepresented minorities.

Analysis

All statistical analyses were conducted using R software (R version 3.0.0, GNU project). To address the primary aim, we used generalized estimating equations (GEE). Generalized estimating equations are a general method for analyzing correlated data that are observed in clusters. We compared outcome measures among people characterized as living with mental illness, physical illness, and in good health. We also explored comparing outcome measures among all illnesses and good health (i.e. compared outcomes of those with schizophrenia, depression or anxiety, cancer, diabetes, HIV, and healthy).

For each domain, we took responses of multiple items (within each domain) as a vector outcome of the GEE model and item indicators, group membership, sex, age, education, race/ethnicity as covariates. We tested two-way interaction terms with item indicators, and kept only significant interaction terms in the model. When no significant differences among group membership resulted, we conducted exploratory sub-analyses within groups. We report coefficient estimates and confidence intervals drawn from the final analytic model for each domain.

As a secondary aim, we sought to clarify whether being in a clinical research protocol may have shaped the perspectives expressed by individuals we queried. We compared responses for each domain among healthy individuals with and without direct experience in clinical research.

RESULTS

Study population characteristics (Table 1)

Our study had 179 participants. Of these, 150 were currently enrolled in clinical research protocols, and 29 were healthy individuals not in clinical research protocols. Of the total, 43% of respondents were living with mental illness (i.e. schizophrenia; depression or

anxiety disorder), 29% with physical illness (i.e. cancer, HIV/AIDS, diabetes), and 31% without illness. The mean (SD) age was 44.5 (13.3) years. A majority of respondents were 56.5% white, and the remainder was of Hispanic (29.9%) or other (13.6%) ethnicities.

Ill and healthy respondents were comparable on the internal health locus scale ($p=0.78$) but as expected, differed in most of the other measures, such as the BSI Global severity ($p<0.001$), the social support ($p<0.001$), SF36 Current health ($p<0.001$), and multidimensional health ($p<0.001$). The groups also differed by ethnicity ($p=0.05$), education ($p=0.01$), and marginally differed by marital status ($p=0.07$).

Domain 1: Ethical acceptability of participation in burdensome and life-threatening research

Overall trends—Respondents on average across groups expressed negative or neutral views regarding the ethical acceptability of participation in research that posed significant burdens, such as causing unpleasant side effects, pain, worsening of symptoms, or life-threatening consequences (Table 2). Of all respondents in this study, a minority indicated that they agree or strongly agree (i.e., rating = 4 or 5) that people should participate in research even if it causes life-threatening consequences (13%, $n=19$), worsening symptoms (23%, $n=34$), unpleasant side effects (27%, $n=40$), or pain (39%, $n=59$).

Respondents expressed decreasing levels of acceptance of participation in research that posed burdens of increasing severity (Figure 1). Participation in protocols with possibly life-threatening consequences was perceived as least acceptable (mean = 1.82, sd = 1.29). Adjusting for confounders, respondents expressed greater acceptance of participation in research causing unpleasant side effects compared to participation in research causing life-threatening consequences ($\beta = 1.35$, 95% CI = [1.13, 1.57]). Respondents expressed greater endorsement for participation causing pain than for participation with life-threatening consequences ($\beta = 0.82$, 95% CI = [0.63, 1.01]) and also expressed greater endorsement for participation causing worsening symptoms than for participation with life-threatening consequences ($\beta = 0.61$, 95% CI = [0.43, 0.79]).

Comparisons by respondent group—For Domain 1, ratings of respondents with mental illness (i.e. schizophrenia or depression or anxiety) regarding ethical acceptability of research were not significantly different from ratings of respondents with physical illness ($\beta = -0.10$, 95% CI = [-0.58, 0.16]) and of respondents in good health ($\beta = -0.31$, 95% CI = [-0.52, -0.10]). Respondents with schizophrenia, for example, endorsed views that did not differ from those expressed by healthy people for all protocol-related burdens, i.e. causing side effects ($\beta = -0.64$, 95% CI = [-1.75, 0.48]), causing pain ($\beta = -0.07$, 95% CI = [-0.72, 0.58]), and causing symptoms to worsen ($\beta = 0.04$, 95% CI = [-1.13, 1.21]), as well as risk, i.e., causing life-threatening implications ($\beta = 0.12$, 95% CI = [-1.02, 1.25]).

Exploratory findings—Other analyses revealed that living with cancer and age were factors in shaping views on ethical acceptability of research. Respondents with cancer expressed greater acceptability for burdensome research on the whole compared to participants in good health ($\beta = 0.86$, 95% CI = [0.21, 1.51]). (Figure 2). Respondents with cancer also expressed greater acceptance of research with life-threatening consequences

when compared with views of healthy individuals, even after adjusting for covariates ($\beta = 0.82$, 95% CI = [0.02, 1.61]). Age was associated with greater agreement of research participation in the context of protocol related burdens. Respondents older than 50 years expressed more agreement of research participation than respondents younger than 50 years of age ($\beta = 0.65$, 95% CI = [0.12, 1.18]).

Association with protocol participation—Protocol participation did not appear to be associated with differences in the attitudes expressed by healthy individuals we interviewed. Healthy respondents enrolled in clinical research protocols and healthy individuals not in protocols expressed similar views on the ethical acceptability of research posing burden and risk ($\beta = 0.21$, 95% CI [-0.14, 0.55]). Among healthy respondents, men found burdensome research to be more acceptable than women did (β , difference between women and men = -0.42, 95% CI = [-0.79, -0.04], p -value=0.03).

Domain 2: Ethical acceptability of serious illness research

Overall trends—Respondents across all groups expressed on average favorable views of the ethical acceptability of research on cancer, HIV, schizophrenia, major depression, and post-traumatic stress disorder (Table 2) (range of means = [4.0, 4.7]). A majority of all respondents indicated that they agree or strongly agree (i.e., rating = 4 or 5) on the ethical acceptability of research involving people with cancer (87%, $n=131$), HIV (87%, $n=130$), schizophrenia (77%, $n=115$), major depression (76%, $n=114$), or post-traumatic stress disorder (77%, $n=115$).

Comparisons by respondent group—Responses on the ethical acceptability varied by respondent group (p -value from MANOVA<0.001). Respondents with mental illnesses, on average, strongly endorsed the ethical acceptability of mental illness research and physical illness research (range of means for acceptability of mental illness research = [4.17, 4.22]). Respondents with mental illness did not view the acceptability of mental illness research different from that of physical illness research ($\beta = -0.07$, 95% CI = [-0.26, 0.13]).

Respondents with mental illness (i.e. schizophrenia or depression or anxiety) expressed levels of acceptance of research participation that were not statistically different from levels expressed by those with physical illness ($\beta = 0.03$, 95% CI = [-0.21, 0.27]) and levels expressed by those in good health ($\beta = 0.09$, 95% CI = [0.00, 0.18]).

Respondents with physical illnesses (cancer, diabetes, or HIV/AIDS) on average expressed greater ethical acceptability of research involving physically ill people than for research involving mentally ill people ($\beta = -0.55$, 95% CI = [-0.81, -0.29]). Healthy protocol volunteers perceived physical illness research and mental illness research as acceptable (range of means = [4.32, 4.57]) but not differential ($\beta = -0.02$, 95% CI = [-0.18, 0.14]).

Exploratory findings—Respondents with cancer endorsed greater ethical acceptability of research participation involving people with physical illness than people with mental illness (β , difference between physical and mental illness = 0.95, 95% CI = [0.40, 1.49]). Furthermore, respondents with cancer endorsed greater ethical acceptability of research involving people with cancer than for research involving people living with other diseases (β

= 0.25, 95% CI = [0.04, 0.47]). Respondents with HIV/AIDS also expressed greater ethical acceptance of research involving people living with HIV than of research involving people with other severe illnesses, i.e. cancer, depression, PTSD, and schizophrenia. (β = 0.32, 95% CI = [0.12, 0.53]). (Figure 3)

Association with protocol participation—For Domain 2, healthy respondents in protocols expressed levels of ethical acceptability of research participation not different from other healthy respondents without experience as clinical research protocol (β = -0.08, 95% CI = [-0.45, 0.29]). Healthy respondents also rated the ethical acceptability of mental illness research on a level that was not significantly different from that of physical illness research (β , difference between mental and physical illness research = -0.09, 95% CI = [-0.33, 0.14]).

Domain 3: Ethical acceptability of research in the context of vulnerability

Overall trends—A large majority of respondents endorsed the acceptability of research involving those who were either sick or dying (87%, n=121), in a lot of physical pain (72%, n=108), or in a lot of emotional pain (67%, n=100). (Table 2). A majority of respondents endorsed acceptability of research involving minority subpopulations (75%, n=112), women of child-bearing age, the poor (66%, n=99), elderly people (65%, n=98), and people living in a facility (64%, n=96). Less than half endorsed acceptability of research involving children (43%, n=64).

A minority of mentally ill participants endorsed research involving subpopulations known to be ill (47%, n=28), while a strong majority of participants who were ill (60%, n= 26) and in good health (66%, n=31) strongly endorsed the acceptability of such research (p-value from chi-squared test = 0.11). A substantial majority of all respondent groups strongly endorsed research involving subpopulations with vulnerabilities related to non-illness related sources, (mentally ill = 65%, n=39, physically ill = 56%, n=24, healthy people = 64%, n=30, p-value from chi-squared test = 0.61).

Mentally ill respondents' ratings of the ethical acceptability of research participation involving vulnerable populations were similar to ratings of healthy respondents (β = -0.04, 95% CI = [-0.46, 0.38]), as well as respondents with physical illness (β = -0.13, 95% CI = [-0.62, 0.36]).

Interestingly all respondents who participated in a clinical protocol, irrespective of health status, endorsed greater ethical acceptability for research involving those known to be ill, i.e. people who were very sick or dying, living in a lot of emotional pain, physical pain, and living in facilities, than for research involving groups who were potentially vulnerable due to non-illness related attributes, i.e. women of child-bearing age, children, elderly, ethnic minorities (β = 0.64, 95% CI = [0.35, 0.93]).

Exploratory findings—We found educational level to be positively associated with attitudes endorsing greater ethical acceptability of research involving vulnerable populations. Respondents with at least a college education expressed greater acceptance of research involving populations that are potentially vulnerable due to illness and non-illness

related sources than those who had some college or less ($\beta = 0.310$, 95% CI = [0.01, 0.59], p -value=0.04). White respondents endorsed greater ethical acceptability of research involving populations with illness-related sources of vulnerability than they did for research involving vulnerable populations by virtue of non-illness-related sources ($\beta = -0.08$, 95% CI = [-0.13, -0.03].)

Association with protocol participation—We found no significant effect of being enrolled in a protocol among healthy respondents. For Domain 3, healthy respondents in protocols expressed levels of ethical acceptability of research participation involving vulnerable populations not significantly different from those expressed by research-naïve respondents ($\beta = -0.18$, 95% CI [-0.46, 0.11]). Unlike the cohort of research volunteers, healthy respondents as a whole endorsed greater acceptability for research involving populations who are vulnerable by virtue of non-illness related sources than those who were known to be ill ($\beta = -0.64$, 95% CI = [-1.19, -0.08]).

DISCUSSION

This empirical report documents the views of clinical research volunteers and healthy individuals regarding the ethical acceptability of human studies in three circumstances: burdensome and life-threatening research; serious illness research; and research involving potentially vulnerable subpopulations. Our study allowed for the comparison of the perspectives held by mentally ill, physically ill, and healthy individuals. Our design also permitted us to test the effect of protocol participation itself through the inclusion of healthy individuals with and without experience in a clinical research protocol. The content, the participants, and the design of our project thus address and may help begin to resolve -- through the use of empirical data -- some of the most highly controversial ethical issues faced in human research.

Participants in this project strongly affirmed the acceptability of human studies in the context of diverse diseases, with especially strong endorsement of the investigation of physical illnesses. Research involving significant burdens, such as adverse effects, pain, and worsening symptoms, and life-threatening risk, was seen as less ethically acceptable. Similarly, the majority of respondents did not endorse research including children as ethically acceptable. Involvement of individuals with other potential vulnerabilities in the research situation was otherwise viewed favorably -- but with nuances suggesting an understanding of the potential for the exploitation of human subjects. Research with people living in a facility or with people who are poor, for instance, was perceived as less ethically acceptable. These responses suggest sensitivity to the role of clinical research, aspects of the illness experience, the risks that protocols may present, and an awareness of the pressures experienced by individuals who have delimited freedoms or needs that may color their decisions to volunteer as human subjects.

Taken together, a remarkable general pattern of agreement in ethical perspectives emerged in this project. The congruence in views across groups represents a noteworthy finding because of the concern that people with mental illness should be viewed differently than other ill individuals, i.e., as an “exception.” Our project included people living with

schizophrenia, depression or anxiety, people living with HIV, cancer, or diabetes, and people in good health, some of whom had been in clinical research and some of whom had not, and the overall findings on key outcomes were similar. Based on our earlier work, we accurately predicted that physically and mentally ill individuals would express similar and positive attitudes toward research. We anticipated that respondents with higher educational levels would express more favorable views, and this prediction was confirmed. We were nevertheless surprised to find that clinical research participation and gender were not consistently associated with different perspectives. For these reasons, we believe these data represent a novel contribution to the published literature – a literature that, in the main, has not sought to explore the views of individuals who shoulder the burdens and accept the risks of clinical research participation in pursuit of scientific knowledge that aims to benefit others.

Some separation of views emerged in relation to perceptions of the ethical acceptability of life-threatening research and research on physical illnesses. Respondents in the physical illness group and, even more specifically, our respondents living with cancer, viewed of protocol participation involving life-threatening risk more favorably than did healthy respondents. This finding fits with the data-based literature documenting that some very seriously physically ill research participants may be especially willing to assume significant dangers in trade for the slim chance of personal benefit, as occurs in some studies.^{11,29–32} In addition, a minority of our participants (13%) indicated that even life-threatening research was completely acceptable, suggesting that there may be some research volunteers who are ‘high risk-takers’ by nature and whose judgments may differ greatly from other participants. With respect to perceptions of physical illness research, respondents with HIV not unexpectedly expressed stronger support for the ethical acceptability of HIV research. And both physically ill and mentally ill respondent groups endorsed physical illness research more than did healthy respondents.

Our results should be interpreted in light of the limitations of the study which include its reliance on self-report items, the engagement of individuals who were on some level receptive to research as evidenced by their consenting to our minimal-risk semi-structured interview study, and the use of a single geographic location. Results from our exploratory aims should also be used as a rationale for further inquiry.

The ethical acceptability of clinical research is an important matter for the public trust. Our findings suggest that individuals with their own immediate experience in protocols view clinical research favorably and see engagement of ill and many other potentially vulnerable people in research as ethically acceptable. We found that people with significant mental illness and physical illness offered perspectives that were nuanced and logical and similar to responses of healthy individuals. These results may help to diminish “exceptionalism” and stigma of mental illness and mental illness investigation^{3,9,13} by providing data that begin to address the theoretical question of whether people with certain illnesses should be viewed as intrinsically different from other research volunteers and/or require additional federal safeguards. The observation that a minority of our respondents found highly dangerous research completely acceptable merits further study and serves as a caution to all investigators to be well-prepared for the professional responsibilities they assume in human

studies and to clarify the risk-taking attitudes and motivations of potential protocol volunteers.^{33–35}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The author expresses appreciation to Teddy Warner, Ph.D., Kate Green Hammond, Ph.D., and Janet L. Brody, Ph.D. The author also wishes to thank Melinda Hantke and Ann Tennier for their assistance in preparing this manuscript.

This IRB-approved project was funded jointly by the National Institute of Mental Health and the National Institute on Drug Abuse.

Role of the Funding Source

This project (1R01MH058102) was funded jointly by the National Institute of Mental Health and the National Institute on Drug Abuse.

The authors express appreciation to Teddy Warner, Ph.D., Kate Green Hammond, Ph.D., and Janet L. Brody, Ph.D., who assisted in the early development of this project. The author also wishes to thank the participants in the project and Melinda Hantke and Ann Tennier for their assistance in preparing this manuscript. The author also thanks George Nurnberg, M.D., John Lauriello, M.D., Sarah Allen, M.D., and Cheryl Willman, M.D.

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Highlights

- We present the views of mentally ill research volunteers and to compare these perspectives with those of physically ill and healthy research participants
- Mentally ill research volunteers strongly endorsed ethical acceptability for physical illness research and mental illness research
- Physically ill volunteers expressed greater ethical acceptability for physical illness research than for mental illness research
- Respondents expressed decreasing levels of acceptance of participation in research that posed burdens of increasing severity
- Mentally ill research volunteers and healthy individuals expressed similar perspectives in this study, helping to dispel a misconception that those with mental illness should be presumed to hold disparate views

Figure 1.

Attitudinal trends on the acceptance of participation in burdensome research by disease group

Responses were rated on a 5-point scale, with “1” indicating “strongly disagree” to “5” indicating “strongly agree.” Participants who were enrolled in clinical research protocols studying cancer, diabetes, HIV, depression or anxiety disorder, schizophrenia, and had verified diagnoses of these conditions, were compared to healthy participants in protocols.

Figure 2.
Respondent views by disease group, regarding the ethical acceptability of burdensome research compared to the benchmark of views expressed by healthy participants

Figure 3.
A comparison of perceived ethical acceptability of physical illness research against the benchmark of perceived acceptability of mental illness research

Table 1

Study Population Characteristics

	Mentally Ill In Protocol N = 60	Physically Ill In Protocol N = 43	Healthy In Protocol N = 47	Healthy Not in Protocol N = 29	P-value
Age (yrs)[†]					
18-35	20% (12)	23% (10)	36% (17)	59% (17)	< 0.001
36-50	62% (37)	35% (15)	19% (9)	28% (8)	
51-60	13% (8)	28% (12)	19% (9)	3% (1)	
61+	2% (1)	14% (6)	26% (12)	10% (3)	
Sex					
Women	67% (40)	56% (24)	45% (19)	55% (16)	0.16
Men	33% (20)	44% (19)	55% (26)	45% (13)	
Marital Status^{††}					
Married (or living w/partner)	38% (23)	44% (19)	68% (32)	45% (13)	0.07
Single	60% (36)	56% (24)	32% (15)	55% (16)	
Race^{††}					
Hispanic	25% (15)	47% (20)	19% (9)	31% (9)	0.05
Other	23% (14)	9% (4)	9% (4)	17% (5)	
White	50% (30)	44% (19)	72% (34)	52% (15)	
Education level^{††}					
Less than HS	15% (9)	12% (5)	0% (0)	0% (0)	0.01
HS	25% (15)	23% (10)	13% (6)	10% (3)	
Some college/vocational training	27% (16)	40% (17)	26% (12)	48% (14)	
College degree	22% (13)	19% (8)	43% (20)	31% (9)	
Graduate degree	10% (6)	7% (3)	19% (9)	10% (3)	
Missing	2% (1)	0% (0)	0% (0)	0% (0)	
Disease type					
Cancer	—	28% (12)	—	—	*
Diabetes	—	33% (14)	—	—	
HIV	—	40% (17)	—	—	
Anxiety mood disorder	42% (25)	—	—	—	

	Mentally Ill In Protocol <i>N</i> = 60	Physically Ill In Protocol <i>N</i> = 43	Healthy In Protocol <i>N</i> = 47	Healthy Not in Protocol <i>N</i> = 29	P-value
Schizophrenia	58% (35)	–	–	–	
BSI global[*]	1.14 (0.86)	0.64 (0.70)	0.28 (0.29)	0.38 ^a (0.38)	< 0.001
Social Support overall	63.15 ^a (23.04)	77.98 (15.41)	82.27 ^a (15.69)	76.36 (21.91)	< 0.001
SF-36: Current health subscale[*]	53.12 (22.11)	49.64 (25.65)	76.81 (19.26)	72.5 (26.59)	< 0.001
MHLOC					
Internal Health Locus [*]	25.57 (5.97)	26.36 (5.51)	25.84 ^a (4.34)	25.89 (5.55)	0.78
Powerful Other Locus [*]	20.86 (7.11)	20.45 (6.62)	16.98 ^a (5.05)	15.93 (6.12)	< 0.001
Chance Locus	19.43 ^b (5.85)	17.38 ^γ (6.47)	15.41 ^γ (4.16)	16.29 ^a (4.83)	< 0.01

[†] Missing observations (m) were excluded from analysis: Mentally ill in protocol *m* = 2;

^{††} Mentally ill in protocol: *m* = 1

^{*} Mentally ill in protocol, Physically ill in protocol: *m* = 4 with exceptions

^a *m* = 7 and

^b *m* = 6; Healthy not in protocol: *m* = 1 with exceptions

^a *m* = 2

^γ *m* = 3

Table 2

Views of protocol participants regarding the ethical acceptability of research participation in three domains

	Respondent group							
	Mentally ill N = 60		Physically ill N = 43		Healthy N = 47		Overall N = 150	
	Mean	(sd)	Mean	(sd)	Mean	(sd)	Mean	(sd)
Domain 1: Burdensome research								
People should participate even if it causes: (0.31 **)								
Pain	2.85	1.34	3.58	1.38	3.17	1.27	3.16	1.36
Unpleasant side effects	2.42	1.39	3.07	1.49	2.53	1.36	2.64	1.43
Symptoms to worsen	2.28	1.44	2.63	1.38	2.40	1.28	2.42	1.37
Life-threatening consequences	1.68	1.33	2.09	1.38	1.77	1.13	1.82	1.29
Domain 2: Serious illness research (<0.001 **)								
HIV	4.17	1.17	4.67	0.57	4.57	0.62	4.44	0.89
Cancer	4.15	1.15	4.58	0.63	4.47	0.78	4.37	0.92
Schizophrenia	4.22	0.98	4.00	1.11	4.38	0.80	4.21	0.97
Post-traumatic stress disorder	4.17	0.99	4.16	1.04	4.32	0.86	4.21	0.97
Major depression	4.10	1.08	4.14	0.97	4.34	0.84	4.19	0.98
Domain 3: Research in the context of vulnerability								
Illness related vulnerability (0.63 **)								
Sick/dying	3.93	1.18	4.03	1.02	4.06	1.11	4.00	1.12
In alot of physical pain	4.05	1.14	4.30	0.96	4.19	1.08	4.17	1.07
In alot of emotional pain	4.00	1.13	4.19	0.79	4.02	1.19	4.06	1.06
Living in a facility	3.88	1.29	3.93	0.94	3.98	1.15	3.93	1.15
Non-illness related vulnerability (0.02 **)								
Minorities	3.78	1.18	3.72	1.28	4.06	1.07	3.85	1.18
Women of child-bearing age	3.56	1.35	3.85	1.24	4.17	0.95	3.84	1.22
Poor	3.75	1.30	4.37	1.02	4.53	0.69	4.17	1.11
Elderly	3.78	1.34	3.88	1.22	4.19	0.88	3.94	1.18
Children	3.65	1.26	4.00	1.07	4.23	0.91	3.93	1.13
	3.65	1.23	3.88	1.16	4.21	0.91	3.89	1.14
	2.99	1.47	3.12	1.40	3.66	1.13	3.24	1.37

* as defined by having responded with a "4" or "5";

[†] strongly endorse at least one item within domain;

** p-values based on MANOVA tests by respondent group.