Points to Consider when Reviewing Research with Vulnerable Populations Not Explicitly Protected in CFR
(from OHRP Institutional Review Board Guidebook: Chapter VI, Special Classes of Subjects)

COGNITIVELY IMPAIRED PERSONS

Does the IRB need to include a member knowledgeable about and experienced with the mentally disabled or cognitively impaired?

Does the research pertain to mental disabilities so that it is necessary to involve persons who are mentally disabled as participants?

If institutionalized individuals will be involved is there sufficient justification for using that population?

Are non-institutionalized persons appropriate for the research and reasonably available?

Does the research pertain to aspects of institutionalization?

Are adequate procedures proposed for evaluating the mental status of prospective participants to determine whether they are capable of consenting?

Are these procedures appropriate both to the participant population and the nature of the proposed research?

Is the risk justified by anticipated benefits to the participants and the importance of the knowledge that may reasonably be expected to result?

Is it possible to identify persons authorized to give consent on behalf of individuals judged incapable of consenting?

Should assent of the prospective participants also be required?

If incapable of giving valid consent, can participants’ objection to participation be overridden?

Under what circumstances?

Should an advocate or consent auditor be appointed to ensure that the preferences of potential participants are elicited and respected?

Should someone ensure the continuing agreement of participants to participate, as the research progresses?

Should the participant’s physician or other health care provider be consulted before he/she is invited to participate in the research?

Is the research likely to interfere with ongoing therapy or regimens?

Is it possible that the request to participate itself might provoke anxiety, stress, or other serious negative response?
Using Social Media in Research: New Ethics for a New Meme?

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The case vignettes presented here highlight ethical issues surrounding the use of social media in clinical research. To date, investigators and institutional review boards (IRBs) have had little in the way of specific guidance in this area. Promulgated more than 30 years ago and amended in 2009, the Code of Federal Regulations for conducting human subjects research does not address social media (45 CFR 46: U.S. Code of Federal Regulations 2009). The U.S. Office for Human Research Protection, in its guidelines issued to address “significant challenges” presented by Internet research, recognized that “ethical conduct of Internet research … brings questions of scientific design into high relief” (U.S. Department of Health and Human Services, Office for Human Research Protections 2013).

The first case, regarding data collection via Facebook, brings up issues of consent, scientific merit, and confidentiality. First, the investigator wonders whether the requirement for informed consent can be waived because viewing publicly accessible Facebook pages is akin to observing public behavior. This may not be the case. The personal use of social media has preexisted its research application; therefore, users may feel that their Facebook page, even if publicly accessible, is still somewhat private and should not be subject to outside scrutiny by others, including researchers. Users may not fully appreciate the privacy risks involved in sharing information (described in more detail in the following), and they may therefore experience an online disinhibition effect (Suler 2004). Online disinhibition may encourage users to act and write in ways that they would find humiliating if observed by the general public or researchers.

Even if research of Facebook activities is considered to be an observation of public behavior within the scope of the Common Rule, it is not necessarily exempt from IRB review. There needs to be a determination of whether (1) the information is recorded in a manner that will allow subjects to be identified and (2) any disclosure of the subjects’ Facebook posts “outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to their financial standing, employability, or reputation” (45 CFR § 46.101(b)(2): U.S. Code of Federal Regulations 2009). This protocol raises questions regarding how the digital information will be recorded, stored, anonymized, and secured, because even if images are obscured to shield identities, investigators may unwittingly stumble upon more data than they had anticipated. Digital photos may contain additional metadata such as the date, time, precise geospatial information about where the photo was taken, and information from or about the device that was used to upload the file, including phone number and device identification. Finally, there is also a risk of liability because, for example, federal law makes it unlawful for minors to possess a handgun or ammunition absent an exemption (Gun Control Act of 1968, 18 U.S.C. § 922(s)(2) 1968).

The scientific merit of this study also comes into question because the online postings being studied may not be a valid source of data—due to the phenomenon of trolling, Internet slang for the practice of purposefully posting inflammatory messages. An Internet troll might make false or unwanted postings under the name of another user or might post untrue opinions simply to be provocative. Furthermore, even if authenticated, the views and attitudes of users of Facebook are not likely to be representative. The use of social media is not evenly distributed across demographics, as research has revealed a digital divide with regard to accessing and navigating health information on the Internet (Viswanath et al. 2013). Thus, finding that a high percentage of young males express positive attitudes regarding gun violence on Facebook may not provide investigators knowledge that is valid or generalizable.

In the second case, investigators wish to use social media to reach a research subject lost to follow-up, a possibility that was not considered during the consent process.

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Contacting the subject in this specific case appears to offer direct, possibly lifesaving benefits to a subject who has expressed a desire to receive that information and may interpret the lack of contact as a sign that all is well. The investigators might plan to inform the IRB of a protocol deviation and send neutrally worded messages to the subject via social media along the lines of “Please contact X for important information as soon as possible.” Such a strategy appears to maximize benefits to the subject while minimizing the risks of loss of privacy.

In this and all cases involving contact between study personnel and subjects via social media, confidentiality issues must be carefully scrutinized, because information shared online contains and creates data that users and researchers may be unaware of. Simply because a user has established an online account does not mean that he or she truly understands the privacy implications. Social media platforms can have onerous terms of service; in some cases, they are contracts of adhesion, meaning that they can be changed unilaterally by the service providers and without notice. The terms of service may give service providers an ownership interest in the information posted, or they may prohibit the data from being used for research altogether. Google’s terms of service, for example, provide Google with a worldwide, perpetual, royalty-free license to content transmitted through their media (Google 2014). Thus, there is virtually no way to guarantee that privacy of online communication can be preserved as it is in the typical clinical research study.

In both cases presented here, ethical problems flourish in the chasm between the goals of clinical research and social media. The goal of social media providers is to commoditize data and maximize its monetary value; they are fixated upon the instrumental value of saleable information. Autonomy, beneficence, and respect for persons are secondary—if not irrelevant—to the bottom line. These are not the goals of the average clinical investigation where researchers are guided to respect the intrinsic value of human subjects. Furthermore, clinical research is a highly regulated enterprise that is slow to change. Coupling it with a rapidly evolving, little-regulated industry has created and will create ongoing problems as investigators, IRBs, and regulators scramble to try to stay informed of changes and create and update protocols and safeguards. Understanding these changes and analyzing their ethical impact requires not only ethicists, but also informaticians and information technology (IT) professionals.

Social media use is a natural evolution of the way people interact and communicate. It is the manifestation of a new meme (defined by Merriam-Webster as an idea, behavior, style, or usage that spreads from person to person within a culture), composed of individual units of cultural transmission, through which information is diffused in novel and sometimes unanticipated ways. The use of social media offers rich data and innovative methods of recruitment and retention—but also some unexpected ethical conundra because like all memes it can take on a life of its own, evolve, replicate, and influence the world of ideas. Thoughtful deliberation is required to keep on track ethically as we find new ways to use social media in health care research.

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REFERENCES


Ethical overkill

Institutions should take a unified look at protections for research on human subjects.

The most important resource needed to conduct research on humans, it is said, is not brainpower or money: it is trust. In the United States, as elsewhere, hundreds of institutions and thousands of investigators work to protect that trust by carefully evaluating proposals for clinical trials and other research that uses human subjects.

Each US institution hosting such a study typically conducts its own ethical review of the proposal. The review process serves many functions: it is an expression of the responsibility that these investigators feel towards protecting their local community, an opportunity to tweak protocols to adapt to the community’s specific needs, and a protection against potential lawsuits resulting from a flawed research protocol.

Sadly, evidence suggests that much of this effort is misplaced. A 2010 survey of 45 institutions reviewing the same protocol found that local scrutiny resulted in no substantial changes (B. Ravina et al. Ann.

Neurol. 67, 258–260; 2010). Instead, most alterations simply inserted standardized institutional language — unrelated to the proposed study — to the informed-consent document signed by research participants before they enter a trial. The total cost of all that review: more than US$100,000.

On 3 December, the US National Institutes of Health (NIH) announced a draft policy intended to reduce that redundancy. Open for comment until 29 January, the proposal would require NIH-funded trials that are conducted at more than one site to be approved by a single institutional review board (IRB), which must be willing to shoulder responsibility for all of the sites. The intention is to speed up the approval process for trials that are conducted at multiple facilities. At present, each site may take a crack at reviewing a protocol, often delaying the start of a trial and introducing potential inconsistencies in study protocols and consent forms at different sites.

The NIH’s move is the latest in a string of efforts by US regulators to change this institutional practice. In 2006, the US Food and Drug Administration released guidance for clinical trials conducted at multiple sites. In it, the agency stated that this ethical review need not take place at every institution. Instead, each trial could designate an institution to conduct a central review for all participating sites.

Four years later, the US Office of Human Research Protections wrote a letter stating its support for that guidance. Despite these assurances, however, it has been difficult to change entrenched institutional practices that have been solidified for more than 40 years.

The NIH’s proposal does not prohibit any participating site from conducting its own review, but clearly frowns on the practice — and explicitly pushes the cost of a duplicate review onto the institution.

Inertia is difficult to overcome, particularly at large institutions and with such a valuable resource at stake. Much of this stubbornness is due to an understandable desire by investigators to protect their patients and community. Some local IRBs fear that abdicating their review of research protocols is a violation of their responsibility to that community, and worry that standards will slip if they do not personally review the study.

“There is no evidence that multiple ethics reviews enhance protections for human subjects.”

As the NIH has said, there is no evidence that multiple ethics reviews enhance protections for human subjects. Centralized review may seem to save time and money, but there is no clear evidence that it protects study subjects any better. Still, the NIH’s move to encourage central review is the right one, given the available evidence.

Regulations that favoured local IRB reviews were developed in an era when studies were typically done at a single site. This is no longer the case. As therapies become more tailored to individual genetics, and diseases are subdivided into rarer subtypes, more sites are needed to enrol enough patients to evaluate an intervention.

Around the world, DNA sequencing labs are generating reams of genetic data that could hold the clues to the next medical revolution. Finding those clues quickly and ethically will require studies that combine data from across the globe. Investigators are clamouring for unified informed-consent documents that will allow them to compile genetic information into databases without creating a legal thicket of differing privacy protections. The NIH’s move is an important step in that direction, but there is much farther to go.
Do investigators understand ethically-important perspectives of clinical research participants? A ‘piggy-back’ study of attunement and alignment in serious illness research

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ABSTRACT

Objective: The authors sought to compare investigators’ predictions of clinical research participants’ attitudes regarding ethically-important considerations in serious illness research with attitudes expressed by participants (“attunement”), to compare the personal attitudes of investigators and clinical research participants (“alignment”), and to explore the association between views expressed and covariates.

Method: The authors queried clinical research participants with either physical or mental illness (n = 100) and faculty investigators conducting the clinical research protocols in which these participants were enrolled (n = 77). Outcomes included attitudes regarding importance of medical research, attributes of seriously ill people in the research situation, and influences on enrollment decisions by seriously ill people. Generalized estimating equations and linear regression models were used.

Results: Investigators underestimated the importance of research about physical illness, mental illness, and healthy people to participants (βH = 0.59, 95% CI [0.36, 0.83]; βM = 0.60, 95% CI [0.27, 0.92]; βH = 0.93, 95% CI [0.57, 1.29]). Investigators incorrectly predicted that participants would assess seriously ill people as more vulnerable in the research situation than participants did (β = −0.38, 95% CI [−1.11, −0.25]). Investigators and participants were aligned on the importance of illness research. Participants expressed greater agreement than investigators regarding the influence of ill individuals indicative of will and cognition in their enrollment decisions (β = 0.69, 95% CI [0.25, 1.13]).

Conclusions: Investigators are attuned to and aligned with research participants in many, but not all, respects. Investigators may bring a protective bias in their predictions of the vulnerabilities of ill volunteers.

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Human studies rely on the mutualism of investigators and participants, who together seek to answer questions of significance to them and to society as a whole. Bioethics principles, such as Respect for Persons, and ethical practices, such as informed consent, presuppose that investigators have an accurate understanding of the views of protocol participants regarding aspects of the research situation (Macklin, 2003; Menikoff, 2009; Roberts and Roberts, 1999; Roberts, 2000; National Bioethics Advisory Commission, 2001; U.S. Department of Health and Human Services, 2011). Failure to appreciate the perspectives of volunteers for clinical research protocols, moreover, may result in exploitation of potentially vulnerable individuals who may not be adequately informed about the aims of clinical investigation and whose hopes for personal benefit may be misplaced in the research situation (the “therapeutic misconception”) (Appelbaum et al., 2004; Lidz et al., 2004; Miller and Brody, 2003; Sugarman et al., 1999; Roberts and Dyer, 2004). Investigators who engage in active and empathic listening are better equipped to recognize when participants are ambivalent, tentative, or even feeling pressured when enrolling in clinical research protocols. Investigators’ accurate understanding of participant views thus may enable a better and comprehensive enactment of human subject safeguards.

Many empirical studies have documented the motivations of protocol volunteers (Sugarman et al., 1999) and yet little is known about the attunement of clinical investigators to the views and
concerns of research participants, so vital to the ethical conduct of human studies (Dunn and Roberts, 2005; Roberts et al., 2004a,b, 2006a,b). To our knowledge, there are no published studies of this topic beyond our own early work which revealed that psychiatric investigators underestimate the positive overall experience, altruistic orientation of volunteers, and level of influence of research staff and/or clinicians who are involved in recruitment as seen by volunteers involved in schizophrenia research (Roberts et al., 2000, 2002; Warner et al., 2003). In this series of studies, we also found that psychiatric investigators underestimated the feeling of hope associated with protocol involvement, as well as the potential for harm encountered in protocols as viewed by volunteers in schizophrenia research. No empirical work to date has examined the attunement of investigators who conduct mental illness or physical illness research to the individuals who may enroll in such protocols (Candlis et al., 2008; Grasso and Appelbaum, 1995;Jeste et al., 2006;Palmer et al., 2005, 2007). Moreover, beyond our own studies, we could find no evidence in the literature regarding whether the personal attitudes toward research held by investigators and prospective volunteers are aligned.

To address this gap in our understanding, we sought to clarify if clinical investigators were attuned to the perspectives expressed by protocol participants regarding the importance of medical research and ethically-salient aspects of research participation and enrollment. We examined how the attitudes expressed may vary in relation to the population being studied, namely, people with serious mental illness, people who are physically ill. We also sought to determine whether investigators and research volunteers were aligned in their personal views of research.

1. Methods

The National Institute of Mental Health and the National Institute on Drug Abuse (1RO1MH058102) funded this IRB-approved project.

1.1. Study population

Adult outpatients and inpatients who agreed to participate in clinical protocols at a university in the southwestern United States and its affiliated VA hospital and had a confirmed diagnosis of schizophrenia, major depressive disorder; anxiety disorder; lung cancer, or advanced HIV-related illness/AIDS were eligible to volunteer for this project. We excluded participants with self-reported active substance use disorders. Protocols varied in their level of risk and in their designs, reflective of clinical research conducted at a mid-sized medical school in a rural state with an active NIH clinical cancer center. Specific information regarding the details of the protocols in which individuals were enrolled was not sought as part of this project.

We conducted interviews for our project within seven days of volunteers' consent to participate in a clinical research protocol. Of 103 clinical research protocol participants who volunteered for this study, we excluded data from three volunteers on the basis of substantially missing values.

Investigators conducting clinical research protocols related to our study's diagnoses were identified through the IRB. All of those who were identified with these protocols were invited to participate in our piggy-back study, amounting to 144 principal investigators and senior staff on research teams. Of these, 99 (69%) responded with completed surveys. We excluded non-faculty investigators (n = 10), as well as respondents with substantially missing values (n = 12), yielding 77 faculty investigators.

All volunteers provided written informed consent.

1.2. Measurement of outcomes

We measured outcomes by 20 attitude items in three domains: (1) the importance of medical research; (2) attributes of seriously ill protocol participants; and (3) influences on seriously ill people in making protocol enrollment decisions.

1.3. Statistical analysis

Our primary aims were to assess investigators' predictions of participant views and views expressed by participants ("attunement") and to assess the personal views of investigators and participants ("alignment") with respect to the three outcome domains. "Alignment" in this project refers to whether or not the average differences are statistically significant.

1.3.1. Outcome definitions

For Domain 1, individuals ranked the importance of medical research about physically ill, mentally ill, and healthy people on a 5-point scale (1 = "not at all important" and 5 = "very important"). For Domain 2, individuals rated agreement on a 5-point scale (1 = "strongly disagree" and 5 = "strongly agree") regarding attributes of seriously ill people in the research situation. For Domain 3, individuals rated agreement on a 5-point scale (1 = "strongly disagree" and 5 = "strongly agree") regarding influences on research enrollment decisions among people living with serious illness.

1.3.2. Tools

We used two sample t-tests and Pearson's Chi-squared tests as appropriate. We compared items within domains with MANOVA tests. We calculated correlation matrices for the outcomes in each survey domain. We used generalized estimating equation models (GEE) with unstructured correlation structures to evaluate the associations between outcome measures and covariates. We performed principal components analysis (PCA) on the outcome vectors for attunement (i.e., investigators' predictions of participant views and participants' views) and alignment (i.e., investigator and participant personal views) in domains 2 and 3. By using PCA, we reduced the high-dimensional data in domains 2 and 3 into a smaller number of important variables ("principal components") that accounted for most of the variance in the data, and were summaries (linear combinations) of the original variables. This method is particularly useful in situations such as ours, where there is measured redundancy in the variables (demonstrated by the correlation matrices). We then assessed associations between principal components and covariates using regression models.

1.3.3. Missing data

In the final data set, outcome data were missing on 10 records. A complete case analysis was performed on 167 records.

1.3.4. Potential confounders

Potential confounders included socio-demographic variables such as age, gender, marital status, and race/ethnicity.

1.3.5. Software

We used R (version 3.0.0, GNU project) for all statistical analyses.

2. Results

2.1. Respondent characteristics (Table 1)

A majority of respondents were male (63%, n = 112); Mean age was 45.6 ± 10.5 years. Of the investigators, 69% had experience focused on physical illness, while 31% had experience focused on
Table 1
Characteristics of study population.

<table>
<thead>
<tr>
<th></th>
<th>Investigators</th>
<th>Clinical research participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 77</td>
<td>N = 100</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>65% (50)</td>
<td>62% (62)</td>
</tr>
<tr>
<td>Women</td>
<td>35% (27)</td>
<td>38% (38)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–35</td>
<td>55% (4)</td>
<td>22% (22)</td>
</tr>
<tr>
<td>36–50</td>
<td>65% (50)</td>
<td>51% (51)</td>
</tr>
<tr>
<td>51–60</td>
<td>22% (17)</td>
<td>20% (20)</td>
</tr>
<tr>
<td>61+</td>
<td>8% (6)</td>
<td>7% (7)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or living w/ partner</td>
<td>87% (67)</td>
<td>42% (42)</td>
</tr>
<tr>
<td>Single</td>
<td>13% (10)</td>
<td>58% (58)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>8% (6)</td>
<td>35% (35)</td>
</tr>
<tr>
<td>Other underrepresented minority</td>
<td>10% (8)</td>
<td>18% (16)</td>
</tr>
<tr>
<td>White</td>
<td>82% (63)</td>
<td>49% (49)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than HS</td>
<td>0% (0)</td>
<td>13% (13)</td>
</tr>
<tr>
<td>High school</td>
<td>0% (0)</td>
<td>25% (25)</td>
</tr>
<tr>
<td>Some college/ vocational school</td>
<td>0% (0)</td>
<td>32% (32)</td>
</tr>
<tr>
<td>College degree</td>
<td>0% (0)</td>
<td>21% (21)</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>100% (77)</td>
<td>9% (9)</td>
</tr>
<tr>
<td>Experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical illness</td>
<td></td>
<td>43% (43)</td>
</tr>
<tr>
<td>Mental illness</td>
<td></td>
<td>57% (67)</td>
</tr>
<tr>
<td>With conducting research about:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical illness</td>
<td>69% (53)</td>
<td></td>
</tr>
<tr>
<td>Mental illness</td>
<td>31% (24)</td>
<td></td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>12% (12)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>14% (14)</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td>17% (17)</td>
</tr>
<tr>
<td>Other mental illness</td>
<td>24% (24)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>33% (33)</td>
<td></td>
</tr>
<tr>
<td>Not applicable</td>
<td>100% (77)</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.001.

mental Illness. Of the respondents, 57% had mental illness and 43% had physical illness.

2.2. Domain 1. Attitudes regarding the importance of medical research (Table 2, Fig. 1)

2.2.1. Attunement

On average, participants and investigators’ predictions of participant views reflected strong endorsement of the importance of medical research. The large majority expressed strong endorsement (rated 4 or 5) of physical illness research (89%, n = 158) and mental illness research (81%, n = 143). A slight majority expressed strong endorsement of the importance of research about healthy people (52%, n = 92).

Investigators consistently underestimated participants’ views of the importance of research on physical illness, mental illness, and health (p-values < 0.001). After adjusting for potential confounders, investigators underestimated participant views on physical illness research (β, difference between participant and investigator means = 0.59, 95% CI [0.36, 0.83]), mental illness research (β = 0.60, 95% CI [0.27, 0.92]), and research about healthy people (β = 0.93, 95% CI [0.57, 1.29]).

Mental illness investigators were better attuned than physical illness investigators regarding the importance of mental illness and physical illness research to participants (SF1). Both investigator groups underestimated participant views of the importance of research about healthy people. Mental illness researchers were well attuned to all participants’ views on mental illness research, whether the participants were living with mental illness (β = −0.14, 95% CI [−0.46, 0.18]) or with physical illness (β = −0.23, 95% CI [−0.94, 0.49]). Moreover, mental illness researchers were also well attuned to the importance of physical illness research, as perceived by physically ill participants (β = −0.49, 95% CI [−1.12, 0.14]).

Physical illness researchers consistently underestimated the importance of research involving ill and healthy people to participants. They greatly underestimated the importance of mental illness research, whether perceived by physically ill volunteers (β = −1.05, 95% CI [−1.68, −0.41]) or mentally ill volunteers (β = −1.13, 95% CI [−1.65, −0.62]), and also underestimated the importance of their own research area as perceived by those who were physically ill (β = −0.72 95% CI [−1.19, −0.24]) or mentally ill (β = −0.58, 95% CI [−1.13, −0.04]).

Gender and age were factors in shaping perspectives on the importance of research on healthy people. Women valued the importance of research about healthy people more than men did (β = 0.48, 95% CI [0.25, 0.84]). Older respondents (>60 years) expressed greater agreement with the importance of research about healthy people than younger respondents (18–35 years) (β = 0.59, 95% CI [0.07, 1.11]).

2.2.2. Alignment

Investigators and participants expressed similar personal views, with the large majority of all respondents strongly endorsing (rated 4 or 5) physical illness research (96%, n = 170), mental illness research (90%, n = 160), and research about healthy people (72%, n = 127). Participants and investigators were aligned in their endorsement of physical illness research (β = 0.08, 95% CI = [−0.08, 0.25]) and mental illness research (β = −0.07, 95% CI = [−0.28, 0.13]), even after adjusting for potential confounders. Investigators endorsed greater importance of research about healthy people than did ill participants (β = −0.45, 95% CI = [−0.65, −0.12]).

Mental illness investigators and participants with mental illness endorsed the importance of mental illness research more than physical illness investigators and participants with physical illness did (β = −0.32, 95% CI = [0.51, −0.13]). Physical illness investigators were aligned with ill participants, whether physically or mentally ill, on mental illness research (β = −0.43, 95% CI = [−0.86, 0]; β = −0.35, 95% CI = [−0.90, 0.21], respectively; see SF2).

Gender and marital status shaped the views expressed about research involving healthy people. Research about healthy people was more important to women than men (β = −0.37, 95% CI [0.17, 0.68]) and single respondents to their married counterparts (β = 0.38, 95% CI [0.19, 0.73]).

2.3. Domain 2. Attitudes regarding attributes of seriously ill people in the research situation (Table 2, Fig. 2)

2.3.1. Attunement

Investigators’ predictions and participants’ views reflected strong endorsement (rated 4 or 5) of the attributes of seriously ill people in the research situation as “more emotionally invested” (71%, n = 126), “more likely to participate” (81%, n = 123), “willing to take risks” (62%, n = 110), and “think more about personal decisions” (50%, n = 89). By contrast, only a minority of investigators’ predictions and participants’ views endorsed the attitude that
Table 2
Views of clinical research participants and investigators regarding three ethically relevant attitude domains.

<table>
<thead>
<tr>
<th>Domain 1: importance of research</th>
<th>N = 100</th>
<th>Investigators' personal views</th>
<th>p-Value</th>
<th>N = 77</th>
<th>Investigators' personal views</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>For people who are:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physically ill</td>
<td>4.83</td>
<td>4.26</td>
<td>&lt;0.001*</td>
<td>4.83</td>
<td>4.74</td>
<td>0.09*</td>
</tr>
<tr>
<td>Mentally ill</td>
<td>4.72</td>
<td>3.92</td>
<td>&lt;0.001</td>
<td>4.72</td>
<td>4.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Healthy</td>
<td>4.03</td>
<td>3.05</td>
<td>&lt;0.001*</td>
<td>4.03</td>
<td>4.23</td>
<td></td>
</tr>
</tbody>
</table>

Domain 2: research participation by seriously ill people

In comparison to healthy people, seriously ill people:

| Are more emotionally involved in their research participation | 3.97 | 4.17 | 0.22 | 3.97 | 4.17 | 0.23 |
| Are more likely to participate in research projects         | 4.00 | 3.83 | 0.30 | 4.00 | 3.73 | 0.10 |
| Are more easily pressured                                   | 2.65 | 3.51 | <0.001 | 2.65 | 3.52 | <0.001 |
| Are too emotionally involved to make good decisions         | 2.22 | 2.61 | 0.02 | 2.22 | 2.56 | 0.05 |
| Are more willing to take risks                              | 3.59 | 3.82 | 0.20 | 3.59 | 3.90 | 0.09 |
| Think more about their personal decisions                    | 3.46 | 3.46 | 0.09 | 3.46 | 3.28 | 0.25 |
| Care more about the wishes of others                        | 2.86 | 2.78 | 0.66 | 2.86 | 2.63 | 0.25 |

Domain 3: Influences on enrollment decisions by seriously ill people

Seriously ill people are influenced by:

| Stress            | 2.78 | 3.74 | <0.001* | 2.78 | 3.90 | <0.001* |
| Physical pain     | 3.16 | 4.09 | <0.001  | 3.16 | 4.05 | <0.001  |
| Emotional pain    | 3.17 | 3.88 | <0.001  | 3.17 | 3.90 | <0.001  |
| Understanding need| 4.13 | 3.57 | <0.001  | 4.13 | 3.78 | 0.04    |
| Feeling like they have no other choice                      | 2.62 | 3.32 | <0.001  | 2.62 | 2.87 | 0.03    |
| Feeling helpless   | 2.75 | 3.39 | <0.001  | 2.75 | 3.18 | 0.02    |
| Feeling despair   | 2.62 | 3.42 | <0.001  | 2.62 | 3.12 | 0.01    |
| Wanting some sense of hope                                 | 3.52 | 4.25 | 0.03    | 3.52 | 4.21 | 0.07    |
| Feeling like they have little to lose                       | 3.50 | 3.74 | 0.19    | 3.50 | 3.45 | 0.01    |
| Having few options for treatment                           | 3.33 | 3.79 | 0.02    | 3.33 | 3.74 | 0.03    |
| Feeling dependent on others                                 | 3.04 | 3.34 | 0.11    | 3.04 | 3.39 | 0.06    |

*p-Values in domain header rows are drawn from MANOVA tests. When MANOVA tests yielded significance, 2-sided t-tests were performed on individual items within the domain.

Seriously ill people are “easily pressured” (38%, n = 68), “too emotionally involved to make good decisions” (14%, n = 24), and “care more about others” (27%, n = 47).

A PCA yielded three principal components for Domain 2, explaining 67% of the variance. We summarize the principal components in terms of the variables with sufficiently “significant” contributions (i.e., weights with absolute value greater than 0.3). The first principal component strongly summarizes nearly all attitudes toward attributes of ill individuals assessed in Domain 2, with the exception of “too emotionally involved to make good decisions.” The second principal component summarizes items suggestive of potential vulnerabilities. The items contributing most to

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Fig. 1. Estimates of attunement and alignment adjusted by covariates for Domain 1/Views regarding the importance of medical research.
this component were attributes of seriously ill people as "[more] easily pressured into participation" and "too emotionally involved to make good decisions about participation," as well as negative weights by optimistic attributes, for example, "likely to participate" and "more invested emotionally in participation." Thus, respondents who viewed seriously ill people as vulnerable have higher values on this component, whereas those who view seriously ill people as possessing optimistic qualities have lower values on this component. The third component summarized items of self-centeredness, in that the factors contributing most were "more emotionally invested in participation," with a negative weight by "care more about others." Respondents who viewed seriously ill people as invested in participation have higher values on this component, whereas respondents who perceived seriously ill people to "care more about the wishes of others" have lower values on this component.

Investigators were well attuned to participant views regarding attributes of seriously ill individuals for the first and third principal components ($\beta = -0.09$, 95% CI $[-0.66, 0.47]$ and $\beta = -0.08$, 95% CI $[-0.42, 0.26]$, respectively). Investigators overestimated the second principal component suggestive of vulnerability in seriously ill individuals as perceived by participants ($\beta$, difference between participant and investigator $= -0.68$, 95% CI $[-1.11, -0.25]$), even after adjusting for confounders.

Age and gender were associated with greater agreement with the items on the attributes of seriously ill individuals. For example, young respondents (aged 18–35 yrs) endorsed more agreement with the third principal component than did the oldest respondents of the cohort (>60 years) ($\beta = -0.57$, 95% CI $[1.30, -0.05]$). Men endorsed greater agreement with the first component than did women ($\beta$, difference between women and men $= -0.56$, 95% CI $[-1.04, -0.08]$).

### 2.3.2 Alignment

Personal views of investigators and participants were well aligned with respect to the first and third principal components ($\beta = 0.03$, 95% CI $[0.54, 0.60]$ and $\beta = 0.28$, 95% CI $[-0.62, 0.06]$, respectively). Investigators expressed greater agreement with attributes of vulnerability than did participants ($\beta$, participant-investigator difference $= -0.75$, 95% CI $[-1.18, -0.32]$).

Gender, age, and race/ethnicity were found to shape perspectives expressed in Domain 2. Although men endorsed greater
agreement with the first principal component than women ($\beta = -0.49$, 95% CI [-0.98, -0.01]), women expressed more agreement than men with the second principal component suggestive of vulnerability attributes ($\beta = 0.38$, 95% CI [0.01, 0.75]). Younger respondents (18–35 years) endorsed greater agreement with the third principal component than did the oldest respondents (>80 years) ($\beta = -0.78$, 95% CI [-1.41, -0.16]), as did whites, who also endorsed greater agreement with the third principal component than did Hispanic respondents ($\beta = 0.51$, 95% CI [0.16, 0.86]).

2.4. Domain 3. Attitudes regarding influences on enrollment decisions of seriously ill people (Table 2, Fig. 3)

2.4.1. Attunement

A majority of investigators' predictions and participants' views reflected a strong endorsement (rated as 4 or 5) of the notion that seriously ill people are influenced in their protocol enrollment decisions by wanting some sense of hope (72%, $n = 128$), understanding the need for research (65%, $n = 115$), feeling as if they have little to lose (59%, $n = 105$), having few options for treatment (56%, $n = 99$), and experiencing pain, whether physical (56%, $n = 100$) or emotional (53%, $n = 94$). Only a minority strongly endorsed the view that seriously ill people are influenced by stress (44%, $n = 78$), having no choice (33%, $n = 58$), feeling helpless (40%, $n = 70$), feeling despair (39%, $n = 69$), or feeling dependent on others (39%, $n = 69$).

A PCA resulted in three principal components for Domain 3, explaining 69% of the variance. The first principal component summarized all influences with the exception of “understanding the need for research.” In the second component, influences on enrollment decisions with sufficiently significant contributions were related to will and cognition (i.e., “understanding the need for research,” “wanting a sense of hope,” “feeling as if they have little to lose”) accompanied by negative weights from attributes of physical discomfort (i.e., stress, physical pain, emotional pain). Thus, respondents who endorse influences related to will and cognition
have higher values on this component, whereas those who endorse influences related to physical discomfort have lower values on this component. The third component encompassed the influences of physical pain, stress, and "understanding the need for research" and the negatively weighted influences of "having no choice" and "feeling helpless."

Investigators overestimated the emphasis that participants placed on the first principal component ($\beta = -1.60, 95\% CI [-2.37, -0.83]$) and overall underestimated the second principal component ($\beta = 0.66, 95\% CI [0.22, 1.09]$). Investigators were well attuned, however, to participants' endorsement of the third principal component ($\beta = 0.10, 95\% CI [-0.28, 0.48]$). Physical illness investigators and participants with physical illness more strongly endorsed the third principal component than did mental illness investigators and participants with mental illness ($\beta = 0.50, 95\% CI [0.12, 0.88]$).

2.4.2. Alignment

Investigators expressed greater agreement than participants with respect to the first principal component. Investigators and participants were aligned in their views concerning influences suggestive of the third principal component ($\beta = -0.10, 95\% CI [-0.47, 0.28]$). Investigators were not aligned with respect to the first principal component ($\beta = -1.45, 95\% CI [-2.22, -0.69]$), and participants expressed greater affirmation of the second principal component than investigators did ($\beta = 0.69, 95\% CI [0.25, 1.13]$).

Mental illness investigators and participants with mental illness endorsed greater agreement with the first principal component than physical illness investigators and participants did ($\beta$, difference between physical and mental illness experience = -0.86, 95\% CI [-1.53, -0.19]). Physical illness investigators and participants with physical illness expressed greater endorsement of the second principal component than did mental illness investigators and participants with mental illness ($\beta = 0.43, 95\% CI [0.05, 0.81]$).

3. Discussion

Ethical research involving human volunteers is predicated on the principle of Respect for Persons. Deep regard for the perspectives, beliefs, and dignity of volunteers is nowhere more salient than in the context of clinical research involving seriously ill individuals who may have many burdens and sources of vulnerability as human subjects. For these reasons, an accurate understanding of the perspectives of protocol participants is critical to the ethical conduct of clinical research. In this project, we sought to understand whether investigators discern the attitudes of clinical research participants — including those living with mental illness or physical illness, or in good health — in their own protocols regarding issues of ethical significance. We further sought to determine whether investigators and participants hold similar personal views regarding ethical considerations in human studies.

Our project demonstrated that investigators consistently underestimated the importance of medical research to participants and predicted incorrectly that physically ill and mentally ill participants would see seriously ill people as highly vulnerable in the research situation. Investigators were also inaccurate in their assessments of the forces present in enrollment decisions — investigators more strongly endorsed the thought that seriously ill people would be seen as affected by worrisome influences, such as stress, physical pain, emotional pain, and feelings of despair, when making enrollment decisions than the participants actually endorsed. More positively, as expected for partners in the mutual effort of clinical research, investigators and participants in their personal views clearly believed in the importance of medical research. Where we found poor attunement or misalignment between volunteers and investigators, there was a pattern in which the volunteers expressed views that were affirming of personal autonomy, optimism, and strength and investigators expressed views that were especially sensitive to the potential vulnerabilities of people living with serious illness.

These main findings confirm our hypotheses and were congruent with past work reflecting the courage and altruism of volunteers and the attentiveness of investigators. Other results of this study, on the other hand, related to the differences in illness type and respondent characteristics were unexpected and warrant additional study. For example, mental illness investigators were better attuned to the views of seriously ill participants, whether physically or mentally ill, regarding the importance of research. Physical illness investigators and people living with physical illness were more sensitive to the effect of certain influences reflective of the exhaustion of emotional resources when deciding to enter research. Women and elders more strongly supported research on healthy people, and individuals living with mental illness were more affirming of all forms of research (i.e., involving physically ill, mentally ill, and healthy participants). We found relatively few differences on the basis of ethnicity.

The strengths of this project are its engagement of seriously ill individuals with real-time experience in clinical research protocols, many of whom were women and underrepresented minorities, and of investigators conducting the protocol investigations. "Piggy-back" studies of this nature are difficult to conduct and produce uniquely valuable data. Our project’s limitations are its self-report bias, small size, and occurrence in a single geographic location. These aspects of the study may limit its generalizability to different populations. Protocol-specific data were not ascertained in this "piggy-back" study, but do merit consideration for future inquiry as such data could be used to examine how views vary in relation to the study-specific risks and benefits. How the measured attitudes shape the enrollment patterns and experiences of volunteers and the behaviors of investigators is also unknown.

This project has many implications for societal stakeholders in addition to investigators and volunteers in clinical research. First, the clinical research participants in our study were individuals living with HIV, cancer, schizophrenia, diabetes, depression, and anxiety — illnesses with tremendous health burdens to individuals and society (Whiteford et al., 2013). These conditions deserve scientific attention to allow for the development of new treatments for individuals and for the benefit of overall public health. Our research participants indicated that they highly value medical research and, in comparison to researchers' predictions, more readily affirmed strengths of seriously ill protocol volunteers and less fully endorsed the negative and coercive influences that may distort decisions to take part in protocols. As we seek to understand this difference, we may ask whether investigators are demonstrating a paternalistic bias in their assessments of participant vulnerability or whether they are being correctly sensitive to the potential for exploitation of ill individuals who become human subjects. Alternatively, rather than emphasizing the "over-estimations" of investigators, should we be more concerned about participants who may be "minimizing" their vulnerability in the context of clinical research, as proponents of the "therapeutic misconception" would suggest? (Appelbaum et al., 2004; Lidz et al., 2004; Miller and Brody, 2003; Sugarman et al., 1999; Roberts and Dyer, 2004). Instead of asserting a definitive interpretation, the point of stakeholder studies such as this project is to demonstrate that there may be different perspectives that must be taken into consideration in matters of shared significance in society (Roberts, 2013). The ethical standing of clinical research in the eyes of people living with serious illnesses, as well as investigators, is one such example.
The observation that investigators and participants hold differing perspectives on serious illness research naturally leads to the question of how stakeholders who are further removed from the research context (e.g., Institutional Review Board members, grant reviewers, and policy makers) may perceive these issues. Attitudes of early career investigators and trainees who later will lead or facilitate clinical research also warrant study, as their attitudes toward ethical considerations may differ from those of their more senior colleagues (Jain et al., 2011a,b; Marrero et al., 2013). Greater understanding of the different points of view fulfills the principle of justice, a precondition for ethically sound research posited by the Belmont Commission but, more concretely, may be particularly vital when stakeholders in funding or regulatory agencies are positioned to make decisions with far-reaching implications for the conduct of human studies.

Our results add to the existing empirical literature on the engagement of ill individuals in clinical research and the self-identified strengths of people with physical and mental illness who choose to be in protocols. For those who are concerned about the proper safeguarding of seriously ill individuals who cannot be exploited in the research situation, our results suggest a protective "bias" of investigators in their understanding of participant perspectives will be reassuring. For those who are concerned about the stigmatizing and disempowering effects of insufficient attunement between investigators and participants, there may be concern about its possible "chilling" effect in the progression of clinical research devoted to devastating diseases. Regardless of one's prior views of the ethics of human studies, our results remind us of the value of exploring and clarifying, rather than presuming, the perspectives of participants who generously volunteer to help find the underpinnings of illness.

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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Conflict of interest

The authors have no conflicts of interest to disclose. Dr. Roberts owns Terra Nova Learning Systems.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.01.012.

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