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Does informed consent given by healthy individuals when enrolling in clinical research feel less voluntary than for ill individuals?

Laura Roberts, Jane Paik Kim*

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA, USA, 94305-5717

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Clinical research is predicated ethically on the authentic voluntarism of individuals who choose to enroll in human studies. Existing literature has focused on aspects of informed consent for clinical research other than voluntarism. The objective of this study was to compare the perspectives of clinical research participants who are in good health and who are ill regarding *voluntarism*-related aspects of informed consent and to assess situational influences that enable voluntarism in the process of obtaining clinical research consent. A 23-item written survey, the Informed Consent Questionnaire (ICQ), was administered in a "piggyback" semi-structured interview study of ill and healthy volunteers enrolled in IRB-approved clinical research studies. A total of 150 (60 mentally ill, 43 physically ill, and 47 healthy) clinical research participants participated. Respondents expressed positive views of their experiences with the informed consent processes for their respective clinical research protocols and respondents strongly endorsed items related to voluntarism irrespective of their illness type (range of means = [3.9, 4.8]). Ill participants more highly endorsed items relating to informed consent conditions (mentally ill vs healthy: 0.54 on a 5-point scale, P value = 0.01) (physically ill vs. healthy: 0.47 on a 5-point scale, P value = 0.01). The favorable views of clinical research participants regarding their experience of giving informed consent to enroll in a study were not surprising. Contrary to our *a priori* hypothesis, healthy individuals did not feel as positively as their ill counterparts.

1. Introduction

Clinical research seeks to better understand and better formulate treatments for serious illnesses that cause great personal suffering and represent a significant burden to public health. Informed consent is fundamental to the ethical conduct of clinical research and is a safeguard practice meant to enable potential volunteers to make knowledgeable, sound, and authentic decisions regarding research study participation (Carpenter et al., 2000; Dunn and Gordon, 2005; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Past empirical work on informed consent has focused primarily on information-sharing and decision-making across a spectrum of illnesses and contexts, which has allowed for the development of improved, more participant-centered practices in obtaining informed consent (Anderson and Mukherjee, 2007; Moser et al., 2006; Roberts, 2000).

Voluntariness is one of the main components of informed consent, but has been perhaps and the least studied empirically and the least well understood conceptually, viewed primarily as individual decisions made in the absence of coercion or undue influence (Roberts, 2002; Appelbaum et al., 2009; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979; Geppert and Abbott, 2007; Christopher et al., 2016). One of us (LWR) has proposed a positive definition of voluntarism as an "individual's ability to act in accordance with one's authentic sense of what is good, right, and best in light of one's situation, values, and prior history" and as having four constituent components that may be assessed in evaluating the quality of informed consent (Roberts, 2002). In this model, voluntarism is "a principle that embodies respect for the person as a human being, as a self with a personal history and values, and as a moral agent with fundamental rights and privileges in our society."

The role of voluntarism in informed consent for research cannot be overstated. Indeed, the commissioners who developed the Belmont Principles of respect for persons, beneficence, and justice articulated that *freedom* to choose to join with researchers to answer a question of significance to humanity was a necessary precondition to ethical investigation involving human participants (Department of Health, Education, and Welfare & National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2014). The commissioners also emphasized the converse: in the absence of

* Corresponding author.
E-mail address: janepkim@stanford.edu (J.P. Kim).

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freedom, in the context of limited rights and autonomy and without safeguards, human studies could not be conducted ethically, as evidenced by historical tragedies in which research was conducted on imprisoned or institutionalized individuals involuntarily (U.S. Advisory Committee on Human Radiation Experiments, 1996; Beecher, 1966). Regulations to protect human subjects, including additional safeguards for individuals with diminished autonomy by context (e.g., those within the judicial system) or by virtue of age (i.e., children), have been created to animate the Belmont Principles in the everyday conduct of clinical research (US Department of Health and Human Services, 2009). Nevertheless, little is known about the lived experience of voluntarism among individuals, both healthy and ill, who choose to enroll in human studies (Roberts, 2002).

To address this gap in knowledge, we designed a "piggyback" study in which we interviewed adults with physical and mental illnesses and adults in good health who had recently chosen to enroll in clinical research at an academic medical center. We sought to assess their experience of voluntarism and their views of relevant influences in the process of giving informed consent in a simple, systematic manner. We also sought to understand whether healthy people, physically ill people, and mentally ill people differed in their experiences and views. We hypothesized, based on our prior work and the extant literature, that healthy and ill individuals would endorse aspects of voluntarism in their enrollment decisions, and that healthy individuals, who by definition have fewer constraints associated with illness, would endorse aspects of voluntarism more robustly.

2. Methods

2.1. Study population

Eligible study participants included volunteers who had recently enrolled in IRB-approved clinical research protocols at University of New Mexico Health Sciences Center and the Albuquerque Veterans Affairs Medical Center. The protocols involved individuals living with anxiety or depression, cancer, diabetes, HIV, or schizophrenia or individuals in good health. Participants with active substance use disorders were excluded from participation based on assessments made by the clinical protocols.

2.2. Survey instrument and data

Based on previous work (Roberts, 2000; Roberts et al., 2006) and the existing research ethics and informed consent literature, a 23-item Informed Consent Questionnaire (ICQ) was created and pilot-tested for this project to assess views of ethically important aspects of clinical research. For this analysis, we focus on four items in the ICQ that assessed perceptions of voluntarism in the consent process for the clinical research protocol and six items in the ICQ that assessed situational influences that enable voluntarism in the consent process for the clinical research protocol.

Respondents were asked to rate the degree to which they agreed or disagreed on a statement concerning their experience with the informed consent procedure they had recently undergone when enrolling in the clinical research protocol on a scale from 1 to 5. Only healthy study participants who had given protocol consent (n = 47) and study participants who had a physical or mental illness (n = 103) and were enrolled in clinical protocol responded to this section of the survey.

2.3. Procedure

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

We obtained written informed consent for our "piggyback" semi-structured interview project. No information from our project was shared with the clinical research teams.

Interviews for our "piggyback" project were conducted within 7 days of participants' informed consent disclosure session for their respective clinical protocols. The survey and interview session was completed, on average, in 1.5–2 h. Participants received $25 compensation.

2.4. Statistical analysis

This analysis focused on 150 individuals who volunteered for this "piggyback" study, 40% (n = 60) of whom were living with mental illness (i.e., schizophrenia, depression, or anxiety disorder), 29% (n = 43) of whom were living with physical illness (i.e., cancer, HIV/AIDS, diabetes), and 31% (n = 47) of whom were in good health.

All statistical summaries and graphical model selection were performed using R software (R version 3.0.0, GNU project). We compared outcome measures among people characterized as living with mental illness, physical illness, and in good health using t-tests, chi-squared tests, and multivariate ANOVA, as appropriate. We used linear regression modeling to explore associations with covariates and item outcomes. We also used generalized estimating equations (GEE) to explore associations between endorsements of the informed consent questionnaire items and participant characteristics when items were multivariate (voluntarism domain and pre-conditions domain). GEE are a general method for analyzing correlated data that are observed in clusters. We also explored comparing outcome measures among all illnesses and good health (i.e., we compared outcomes of those with schizophrenia, depression or anxiety, cancer, diabetes, HIV, and those in good health).

3. Results

3.1. Characteristics of study population

One hundred and fifty participants were enrolled in ongoing clinical research protocols. A total of 85 men and 65 women participated, with half reporting their marital status as single (n = 75) and half reporting as married (n = 74). The healthy and ill groups differed by ethnicity (P value = 0.01), education (P value = 0.02), and by marital status (P value = 0.025); demographic characteristics are presented in Table 1.

Illness, social support, and quality of life background assessments are presented in Table 2a. As expected, ill participants scored higher overall on the Global Severity Index (1.93 vs 1.28) when compared to healthy participants. Overall, healthy participants reported higher levels of social support and quality of life compared to ill participants (as measured by subscales of the Social Support Survey instrument, 80.9 vs 65.8 and 15.3 vs 12.8).

3.2. Domain 1. Voluntarism: comparison of informed consent questionnaire items relating to voluntarism

Respondents expressed positive views of their experiences with the informed consent processes for their respective clinical research protocols and strongly endorsed items related to voluntarism irrespective of their illness type (range of means = [3.9, 4.8]), as shown in Table 2b. Overall, healthy and ill respondents highly endorsed the items with positive-valence suggesting autonomy: "I feel I have a choice about whether to drop out" (means 4.8 for both healthy and ill, respectively) and "the researcher tried to make sure I felt comfortable" (means 4.5 and 4.7 for healthy and ill, respectively).

The degree of endorsement across the ill and healthy respondent groups differed for two items directly assessing perceptions of voluntarism in the clinical research consent process. With respect to the item related to authentic motivation, "the researcher tried to make sure that I really wanted to be in the study," ill respondents expressed a greater degree of endorsement than healthy respondents (4.35 vs 3.91, P value = 0.03). With respect to the negative-valence item "I did not